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

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

Citation

Published Version
doi:10.1016/j.ygyno.2015.04.034

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:33840791

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Open Access Policy Articles, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#OAP
No clinical utility of KRAS variant rs61764370 for ovarian or breast cancer

A full list of authors and affiliations appears at the end of the article.

Abstract

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

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

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

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

**Keywords**

KRAS variant; Breast cancer; Ovarian cancer; Genetic association; Clinical outcome

---

*Corresponding author at: Duke Cancer Institute, Duke University Medical Center, Box 3079, Durham, NC 27710, USA. Tel.: +1 919 684 4943; fax: +1 919 684 8719. berch001@mc.duke.edu (A. Berchuck).

1 Equal contributions.

**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.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at [http://dx.doi.org/10.1016/j.ygyno.2015.04.034](http://dx.doi.org/10.1016/j.ygyno.2015.04.034).
1. Introduction

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

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

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

It has also been reported, based on 232 women with both primary ovarian and breast cancer, that the frequency of the G allele at rs61764370 was increased for those who were screened negative for BRCA1 and BRCA2 (92 cases), particularly among those enrolled within two years of their ovarian cancer diagnosis (to minimize survival bias, 30 cases), those diagnosed with post-menopausal ovarian cancer (63 cases), those with a family history of ovarian or breast cancer (24 cases), and those with a third primary cancer (16 cases) [4].
This notable lack of consistency in findings between studies might be expected when appropriate levels of statistical significance are not used to declare positive findings from multiple small subgroup comparisons or post-hoc hypotheses [19]. In this respect, the dangers of subgroup analyses in the context of clinical trials are well-recognized [20]. These are important caveats, particularly since a genetic test for rs61764370 is currently marketed in the US for risk prediction testing to women who are at increased risk for developing ovarian and/or breast cancer or women who have been diagnosed with either ovarian or breast cancer themselves [21]. In general, much larger studies, with sufficient power to detect positive findings at much more stringent levels of statistical significance ought to be required to establish the clinical validity of a genetic test. Therefore, we conducted centralized genotyping of rs61764370 and other variants in the genomic region around the KRAS gene in 140,012 women to examine associations with risk and clinical outcome of ovarian and breast cancer.

2. Methods

2.1. Study participants

The following three consortia contributed to these analyses: the Ovarian Cancer Association Consortium (OCAC: 41 studies, Supplementary Table S1) [22], the Breast Cancer Association Consortium (BCAC: 37 studies, Supplementary Table S2) [23], and the Consortium of Modifiers of BRCA1 and BRCA2 (CIMBA: 55 studies, Supplementary Table S3) [24,25]. OCAC and BCAC consisted of case–control studies of unrelated women, and CIMBA consisted of studies of women with germline deleterious BRCA1 or BRCA2 mutations primarily identified through clinical genetics centers. For the purpose of the current analyses, only participants of European ancestry were included. Following genotyping, quality control exclusions (described below), and analysis-specific exclusions, data from the following women were available for analysis: 46,173 OCAC participants (15,357 patients with invasive epithelial ovarian cancer and 30,816 controls), 71,170 BCAC participants (33,530 patients with invasive breast cancer and 37,640 controls), and 22,669 CIMBA participants (for ovarian cancer analyses: 2332 affected and 12,433 unaffected BRCA1 carriers, 599 affected and 7305 unaffected BRCA2 carriers; for breast cancer analyses: 7543 affected and 7222 unaffected BRCA1 carriers, 4138 affected and 3766 unaffected BRCA2 carriers). For OCAC, overall and progression-free survival data were available for 3096 patients from 13 studies. Overall survival data were available for 28,471 patients from 26 BCAC studies and for 2623 mutation carriers with breast cancer from 11 CIMBA studies (excluding studies with less than ten deaths) as described previously [26,27]. Each study was approved by its relevant governing research ethics committee, and all study participants provided written informed consent.

2.2. Genotyping and imputation

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

In addition to rs61764370, 54 variants within 100 kb on either side of KRAS on chromosome 12 (25,258,179 to 25,503,854 bp in GRCh37.p12) were genotyped. Moreover, to provide a common set of variants across the region for analysis in all the data sets, we also used imputation to infer genotypes for another 1056 variants and for variants that failed genotyping. We performed imputation separately for OCAC samples, BCAC samples, BRCA1 mutation carriers, BRCA2 mutation carriers, and for each of the OCAC GWAS. We imputed variants from the 1000 Genomes Project data using the v3 April 2012 release as the reference panel [30]. To improve computation efficiency we initially used a two-step procedure, which involved pre-phasing using the SHAPEIT software [31] in the first step and imputation of the phased data in the second. We used the IMPUTE version 2 software [32] for the imputation for all studies with the exception of the US GWAS for which we used the MACH algorithm implemented in the minimac software version 2012.8.15 and MACH version 1.0.18 [33]. We excluded variants from association analyses if their imputation accuracy was r² < 0.30 or their MAF was <0.005, resulting in 974 variants genotyped and imputed for OCAC, 989 variants genotyped and imputed for BCAC, and 1001 variants genotyped and imputed for CIMBA, including rs61764370 (Supplementary Tables S5, S6, and S7).

2.3. Analysis

Genotypes were coded for genotype dosage as 0, 1, or 2, based on the number of copies of the minor allele. For ovarian cancer case–control analysis (i.e., OCAC studies), logistic regression provided estimated risks of invasive epithelial ovarian cancer with odds ratios (ORs) and 95% confidence intervals (CIs) adjusting for study, age, and the five European PCs. Subgroup analyses were conducted by histology, family ovarian and breast cancer history, menopausal status, time between ovarian cancer diagnosis and recruitment, and history of multiple primary cancers. For breast cancer case–control analysis (i.e., BCAC studies), the association between genotype and invasive breast cancer risk was evaluated by logistic regression, adjusting for study, age, and the seven European PCs, providing ORs and 95% CIs. Additional subgroup analyses were based on receptor status, first-degree family ovarian and breast cancer history, BRCA1 and BRCA2 mutation status, enrollment within two years of diagnosis, menopausal status (i.e. last menstruation longer than twelve months
ago), age at diagnosis less than 52 years, and history of hormone replacement therapy use (i.e. longer than twelve months use). Risk analysis for \textit{BRCA1} and \textit{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, and residual disease after debulking surgery, and stratified by study, left truncating at the date of study entry and right censoring at five years to minimize events due to other causes. Progression-free survival was analyzed as for overall survival, but without adjustment for age and right censoring, and was defined as the time between the date of histologic diagnosis and the first confirmed sign of disease recurrence or progression, based on GCIG (Gynecological Cancer InterGroup) criteria [36]. We also performed subgroup analysis of patients suboptimally debulked after cytoreductive surgery (residual disease >1 cm) and of post-menopausal patients (age at diagnosis >52 years). Survival analysis of BCAC patients used Cox proportional hazard models estimating HRs and 95% CIs considering overall and breast cancer-specific survival following breast cancer diagnosis. Models were adjusted for age at diagnosis, tumor size, nodal status, grade, adjuvant hormonal and/or chemotherapy, and stratified by study, left-truncating at the date of study entry and right censoring at ten years. In addition, we performed subgroup analysis on ER-positive and ER-negative patients. For CIMBA breast cancer patients associations between genotype and overall survival were evaluated using Cox proportional hazard models estimating HRs and 95% CIs. Models were adjusted for age at diagnosis, tumor size, nodal status, grade, adjuvant hormonal and/or chemotherapy, and preventive bilateral oophorectomy and stratified by study, left-truncating at the date of study entry and right censoring at twenty years. Analyses were performed using STATA version 12.0 (StataCorp, Texas, USA).

3. Results

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

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

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

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

4. Discussion

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

Our study has notable strengths. The vast majority (i.e. >95%) of the samples were genotyped using the same genotyping platform and employing a common approach to genotype calling and quality control; additional samples used denser arrays and nearly identical procedures. The very large sample sizes for all the major phenotypes of interest provide substantial statistical power to exclude any clinically relevant associated risks for the major phenotypes of interest (Fig. 2). The null results found here are thus not due to lack of statistical power, and this analysis also had greater than 80% power to detect association for most of the subgroups, although for some subgroups it was not possible to exclude modest risks. In contrast to the current findings, other genetic association analyses using the same genotyping platform and the same studies as included here have identified more than 90 common germline variants associated with ovarian or breast cancer risk at $p < 5 \times 10^{-8}$ [22,23,37]. While critiques on a previous null KRAS report have suggested that inclusion of male controls, use of “prevalent” cases, and reliance on a surrogate genetic variant may have led to falsely negative conclusions, these are not issues in the present data set. Rather, we demonstrate the importance of international collaboration to identify true associations as well as to refute false associations, an equally important objective.

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

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Authors**

Ovarian Cancer Association Consortium, Breast Cancer Association Consortium, and Consortium of Modifiers of *BRCA1* and *BRCA2*, Antoinette Hollestellea,1, Frederieke H. van der Baanb,1, Andrew Berchuckc,1, Sharon E. Johnattyd, Katja K. Abene,1, Bjarni A. Agnarssonf,1, Kristiina Aittomäkhi, Elisa Alduccil, Irene L.
Andrulis\(^{i,k}\), Hoda Anton-Culver\(^{j}\), Natalia N. Antonenkov\(^{m}\), Antonis C. Antoniou\(^{n}\), Carmel Apicella\(^{o}\), Volker Arndt\(^{p}\), Norbert Arnold\(^{q}\), Banu K. Arun\(^{s,t}\), Brita Arver\(^{r}\), Alan Ashworth\(^{u}\), Australian Ovarian Cancer Study\(^{w,x}\), Laura Baglietto\(^{y,z}\), Rosemary Bailleine\(^{aa}\), Elisa V. Bandera\(^{ab}\), Daniel Barrowdale\(^{a}\), Yukie T. Bean\(^{ac,ad}\), Lars Beckmann\(^{ae}\), Matthias W. Beckmann\(^{af}\), Javier Benitez\(^{ag,af,ai}\), Andreas Berger\(^{aj}\), Raanan Berger\(^{ak}\), Benoit Beuselinck\(^{al}\), Maria Bisogna\(^{am}\), Line Bjørge\(^{an,ao}\), Carl Blomqvist\(^{ap}\), Natalia V. Bogdanova\(^{aq,ar}\), Anders Bojesen\(^{as}\), Stig E. Bojesen\(^{at,au}\), Manjeet K. Bolla\(^{av}\), Bernardo Bonanni\(^{aw}\), Judith S. Brand\(^{ax}\), Hilfrud Brauch\(^{ay,az,aiy}\), Breast Cancer Family Register\(^{ba}\), Hermann Brenner\(^{bp}\), Louise Brinton\(^{bb}\), Angela Brooks-Wilson\(^{bc,bd}\), Fiona Bruinsma\(^{o,y,z}\), Joan Brunet\(^{be}\), Thomas Brüning\(^{bf}\), Agnieszka Budziłowska\(^{bg}\), Clareann H. Bunke\(^{bh}\), Barbara Burwinkel\(^{bi,bj}\), Ralf Butzow\(^{bk,bl}\), Saundra S. Buyu\(^{bm}\), Maria A. Caligo\(^{bn}\), Ian Campbell\(^{bo,bp,bq}\), Jonathan Carter\(^{br}\), Jenny Chang-Claude\(^{bs}\), Stephen J. Chanock\(^{bb}\), Kathleen B.M. Claes\(^{bt}\), J. Margriet Collée\(^{bu}\), Linda S. Cook\(^{bv}\), Fergus J. Couch\(^{bw,bx}\), Angela Cox\(^{by}\), Daniel Cramer\(^{bz,ca,iz}\), Simon S. Cross\(^{cb}\), Julie M. Cunningham\(^{bx}\), Cezary Cybulski\(^{cc}\), Kamila Czene\(^{aw}\), Francesca Damiolo\(^{cd}\), Agnieszka Dansonka-Mieszkowska\(^{bg}\), Hatef Darabi\(^{aw}\), Miguel de la Hoya\(^{ce}\), Anna deFazio\(^{x,cf}\), Joseph Dennis\(^{ch}\), Peter Devilee\(^{cg,ch}\), Ed M. Dickens\(^{cl}\), Orland Diez\(^{cj}\), Jennifer A. Doherty\(^{ck}\), Susan M. Domchek\(^{cl,cm}\), Cecilia M. Dorphling\(^{cn}\), Thilo Dörk\(^{aq}\), Isabel Dos Santos Silva\(^{co}\), Andreas du Bois\(^{so,cd}\), Martine Dumont\(^{cf}\), Alison M. Dunninan\(^{di}\), Mercedes Duran\(^{fs}\), Douglas F. Easton\(^{n,ci}\), Diana Eccles\(^{cl}\), Robert P. Edwards\(^{cu}\), Hans Ehrenrcura\(^{cv}\), Bent Ejertsen\(^{cw}\), Arif B. Ekić\(^{cx}\), Steve D. Ellis\(^{n}\), EMBRACE\(^{c}\), Christoph Engel\(^{cy}\), Mikael Eriksson\(^{aw}\), Peter A. Fasching\(^{df,cz}\), Lidia Feliubadalo\(^{da}\), Jonine Figueroa\(^{ab}\), Dieter Flesch-Jany\(^{sb}\), Olivia Fletcher\(^{ui}\), Annette Fontaine\(^{dc,dd}\), Stefano Fortuzzi\(^{de,df}\), Florentia Fostira\(^{dq}\), Brooke L. Fridley\(^{dh}\), Tara Frie\(^{de}\), Eitan Friedman\(^{di,dk}\), Grace Friel\(^{di}\), Debra Frost\(^{dl}\), Judy Garber\(^{dm}\), Montserrat García-Closas\(^{ui}\), Simon A. Gayther\(^{dn}\), GEMO Study Collaborators\(^{dc}\), GENICA Network\(^{ax,ay,az,bf,dp,dd,dr,ds,dy}\), Aleksandra Gentry-Maharaj\(^{df}\), Anne-Marie Gerdes\(^{du}\), Graham G. Giles\(^{o,y,z}\), Rosalind Glasspool\(^{dv}\), Gord Glendon\(^{dw}\), Andrew K. Godwin\(^{dx}\), Marc T. Goodman\(^{dy}\), Martin Gore\(^{dz}\), Mark H. Greene\(^{es}\), Mervi Grip\(^{eb}\), Jacek Gronwald\(^{ec}\), Daphne Gschwantler Kaulich\(^{el}\), Pascal Guénél\(^{ed,ee}\), Starr R. Guzman\(^{bw}\), Lothar Haeberle\(^{ef}\), Christopher A. Haiman\(^{dn}\), Per Hall\(^{aw}\), Sandra L. Halverson\(^{ef}\), Ute Hamann\(^{ds}\), Thomas V.O. Hansen\(^{eg}\), Philipp Harter\(^{cp,cq}\), Jaana M. Hartikainen\(^{eh,ei}\), Sue Healey\(^{d}\), HEBON\(^{ej}\), Alexander Hein\(^{ek}\), Florian Heitz\(^{cp,cq}\), Brian E. Henderson\(^{dn}\), Josef Herzog\(^{dc}\), Michelle A. T. Hildebrandt\(^{el}\), Claus K. Heggdal\(^{em}\), Estrid Heggdal\(^{en,eo}\), Frans B.L. Hogervorst\(^{ep}\), John L. Hopper\(^{e}\), Keith Humphreys\(^{aw}\), Tomasz Huzarski\(^{ec}\), Evgeny N. Imyanitov\(^{eq}\), Claudine Isaacs\(^{er}\), Anna Jakubowska\(^{ec}\), Ramunus Janavicius\(^{es}\), Katarzyna Jaworska\(^{ec,et}\), Allan Jensen\(^{en}\), Uffe Birk Jensen\(^{eu}\), Nichola Johnson\(^{ui}\), Arja Jukkola-Vuorinen\(^{ev}\), Maria Kabisch\(^{ds}\), Beth Y. Karlan\(^{ew}\), Vesa Kataja\(^{ei,ex}\), Noah Kauf\(^{ff}\), KConFab Investigators\(^{gz}\), Linda E. Kelemen\(^{fa,fb,fc}\), Michael J. Kerin\(^{id}\), Lambertus A. Kiemenev\(^{le}\), Susanne K. Kjær\(^{em,en}\), Julia A. Knight\(^{fl,fq}\), Jacoba P. Knol-Bout\(^{lt}\), Irene Konstantopoulou\(^{dq}\), Veli-Matti Kosma\(^{eh,ei}\), Camilla Krakstad\(^{an,ao}\), Vessela Kristensen\(^{fh,fl}\), Karoline B. Kuchenbaecker\(^{hn}\), Jolanta Kupryjanczyk\(^{kg}\), Yael Laitman\(^{dj,dk}\), Diether Lambrechts\(^{fl,fk}\), Sandrina Lambrechts\(^{fl,fm}\), Melissa C. Larson\(^{fn}\), Adriana Lasal\(^{lo}\), Pierre Laurent-Puig\(^{ho}\), Conxi Lazaro\(^{da}\), Nhu D. Le\(^{ld}\), Loic Le
Affiliations

aDepartment of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands  
bDepartment of Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands  
cDuke Cancer Institute, Duke University Medical Center, Durham, NC, USA  
dDepartment of Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia  
eComprehensive Cancer Center The Netherlands, Utrecht, The Netherlands  
fDepartment for Health Evidence, Radboud University Medical Centre, University of Nijmegen, The Netherlands  
gLandspitali University Hospital, Reykjavik, Iceland  
hDepartment of Clinical Genetics, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland  
iImmunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy  
jDepartment of Molecular Genetics, University of Toronto, Toronto, ON, Canada  
kOntario Cancer Genetics Network, Fred A. Litwin Center for Cancer Genetics, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada  
lDepartment of Epidemiology, University of California Irvine, Irvine, CA, USA  
mN.N. Alexandrov Research Institute of Oncology and Medical Radiology, Minsk, Belarus  
Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK  
Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia  
Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany  
Department of Gynecology and Obstetrics, University Hospital of Schleswig-Holstein, University Kiel, Kiel, Germany  
Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA  
Clinical Cancer Genetics, University of Texas MD Anderson Cancer Center, Houston, TX, USA  
Department of Oncology, Karolinska University Hospital, Stockholm, Sweden  
Breakthrough Breast Cancer Research Centre, Division of Breast Cancer Research, The Institute of Cancer Research, London, UK  
Cancer Division, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia  
Peter MacCallum Cancer Institute, Melbourne, VIC, Australia  
Center for Cancer Research, University of Sydney at Westmead Millennium Institute, Sydney, Australia  
Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, VIC, Australia  
Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia  
Western Sydney and Nepean Blue Mountains Local Health Districts, Westmead Millennium Institute for Medical Research, University of Sydney, Sydney, Australia  
Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA  
Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR, USA  
Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA  
Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany  
University Breast Center Franconia, Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen, Germany  
Centro Nacional de
Genotipación, Human Cancer Genetics Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

Human Genetics Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain

Department of Obstetrics and Gynecology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

Sheba Medical Center, Tel Aviv, Israel

Multidisciplinary Breast Center, University Hospital Leuven, University of Leuven, Belgium

Gynecology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway

Department of Clinical Science, University of Bergen, Bergen, Norway

Department of Oncology, University of Helsinki, Helsinki University Central Hospital, Helsinki, Finland

Department of Obstetrics and Gynaecology, Hannover Medical School, Hannover, Germany

Department of Radiation Oncology, Hannover Medical School, Hannover, Germany

Department of Clinical Genetics, Vejle Hospital, Vejle, Denmark

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

Division of Cancer Prevention and Genetics, Istituto Europeo di Oncologia (IEO), Milan, Italy

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany

University of Tübingen, Tübingen, Germany

German Cancer Consortium (DKTK), Heidelberg, Germany

Department of Epidemiology, Cancer Prevention Institute of California, Fremont, CA, USA

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Genome Sciences Centre, BC Cancer Agency, Vancouver, BC, Canada

Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, BC, Canada

Genetic Counseling Unit, Hereditary Cancer Program, IDIBGI-Catalan Institute of Oncology, Girona, Spain

Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum (IPA), Bochum, Germany

Department of Pathology and Laboratory Diagnostics, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland

Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA

Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany

Molecular Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany

Department of Pathology, Helsinki University Central Hospital, Helsinki, Finland

Department of Obstetrics and Gynecology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland

Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA

Section of Genetic Oncology, Department of Laboratory Medicine, University Hospital of Pisa, University of Pisa, Pisa, Italy

Cancer Genetics Laboratory, Research Division, Peter MacCallum Cancer Centre, Melbourne, Australia

Sir Peter MacCallum

Gynecol Oncol. Author manuscript; available in PMC 2017 May 01.
Department of Oncology, The University of Melbourne, Australia
Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
Center for Medical Genetics, Ghent University, Ghent, Belgium
Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands
Division of Epidemiology and Biostatistics, University of New Mexico, Albuquerque, NM, USA
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
Sheffield Cancer Research Centre, Department of Oncology, University of Sheffield, Sheffield, UK
Obstetrics and Gynaecology Epidemiology Center, Brigham and Women's Hospital, Boston, MA, USA
Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
Academic Unit of Pathology, Department of Neuroscience, University of Sheffield, Sheffield, UK
International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical Academy, Szczecin, Poland
INSERM U1052, CNRS UMR5286, Université Lyon 1, Centre de Recherche en Cancérologie de Lyon, Lyon, France
Molecular Oncology Laboratory, Hospital Clinico San Carlos, Madrid, Spain
Department of Gynaecological Oncology, Westmead Hospital, Sydney, Australia
Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands
Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands
Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK
Oncogenetics Laboratory, University Hospital Vall d’Hebron, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain
Section of Biostatistics and Epidemiology, The Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
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
Department of Genetics, University of Pretoria, Pretoria, South Africa
Non-Communicable Disease Epidemiology Department, London School of Hygiene and Tropical Medicine, London, UK
Department of Gynecology and Gynecologic Oncology, Dr. Horst Schmidt Klinik Wiesbaden, Wiesbaden, Germany
Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany
Centre Hospitalier Universitaire de Québec Research Center, Laval University, Quebec, Canada
Institute of Biology and Molecular Genetics, Universidad de Valladolid (IBGM-UVA), Valladolid, Spain
Faculty of Medicine, University of Southampton, University Hospital Southampton, Southampton, UK
Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Gynecologic Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
Department of Clinical Genetics, Lund University, Lund, Sweden
Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
Institute of Human Genetics, Friedrich Alexander University Munich, Munich, Germany

Gynecol Oncol. Author manuscript; available in PMC 2017 May 01.
University Erlangen-Nuremberg, Erlangen, Germany
Department of Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany
David Geffen School of Medicine, Department of Medicine, Division of Hematology and Oncology, University of California at Los Angeles, CA, USA
Diagnostic Unit, Hereditary Cancer Program, IDIBELL-Catalan Institute of Oncology, Barcelona, Spain
Department of Cancer Epidemiology/Clinical Cancer Registry, Institute for Medical Biometrics and Epidemiology, University Clinic Hamburg-Eppendorf, Hamburg, Germany
Clinical Cancer Genetics, City of Hope, Duarte, CA, USA
New Mexico Cancer Center, Albuquerque, NM, USA
Fondazione Istituto di Oncologia Molecolare (IFOM), Milan, Italy
Cogentech Cancer Genetic Test Laboratory, Milan, Italy
Molecular Diagnostics Laboratory, Institute of Nuclear & Radiological Sciences & Technology, Energy & Safety, National Centre for Scientific Research Demokritos, Aghia Paraskevi Attikis, Athens, Greece
Kansaski IDeA Network of Biomedical Research Excellence Bioinformatics Core, The University of Kansas Cancer Center, Kansas City, KS, USA
University of Pennsylvania, Philadelphia, PA, USA
The Susanne Levy Gertner Oncogenetics Unit, Sheba Medical Center, Tel-Hashomer, Israel
Institute of Oncology, Sheba Medical Center, Tel-Hashomer, Israel
Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA
Center for Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Boston, MA, USA
Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
GEMO Study: National Cancer Genetics Network, UNICANCER Genetic Group, France
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
Gynaecological Cancer Research Centre, Department of Women's Cancer, Institute for Women's Health, UCL, London, UK
Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
Cancer Research UK Clinical Trials Unit, The Beatson West of Scotland Cancer Centre, Glasgow, UK
Ontario Cancer Genetics Network, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada
Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, KS, USA
Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center, Los Angeles, CA, USA
Gynecological Oncology Unit, The Royal Marsden Hospital, London, UK
Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA
Department of Surgery, Oulu University Hospital, University of Oulu, Oulu, Finland
Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
INSERM U1018, CESP (Center for Research in Epidemiology and Population Health), Environmental Epidemiology of Cancer, Villejuif, France
University Paris-Sud, UMRS 1018, Villejuif, France
Division of Epidemiology,
Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA 

Department of Genomic Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark 

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 

The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON), Coordinating Center: Netherlands Cancer Institute, Amsterdam, The Netherlands 

University Hospital Erlangen, Department of Gynecology and Obstetrics, Friedrich-Alexander-University Erlangen-Nuremberg, Comprehensive Cancer Center, Erlangen, Germany 

Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA 

Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark 

Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark 

Molecular Unit, Department of Pathology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark 

Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands 

N.N. Petrov Institute of Oncology, St. Petersburg, Russia 

Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA 

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 

Postgraduate School of Molecular Medicine, Warsaw Medical University, Warsaw, Poland 

Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark 

Department of Oncology, Oulu University Hospital, University of Oulu, Oulu, Finland 

Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA 

Jyväskylä Central Hospital, Jyväskylä, Finland 

Clinical Genetics Research Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY, USA 

kConFab: Kathleen Cuningham Consortium for Research into Familial Breast Cancer — Peter MacCallum Cancer Center, Melbourne, Australia 

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 

School of Medicine, National University of Ireland, Galway, Ireland 

Department of Urology, Radboud University Medical Centre, Nijmegen, The Netherlands 

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 

Department of Genetics, Institute for Cancer Research, Oslo University Hospital, Radium hospitalet, Oslo, Norway 

Faculty of Medicine (Faculty Division Ahus), Universitetet i Oslo, Norway 

Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Belgium 

Vesalius Research Center (VRC), VIB, Leuven, Belgium 

Division of Gynecologic Oncology, Department of
Obstetrics and Gynaecology, University Hospitals Leuven, Leuven, Belgium
Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA
Genetic and Molecular Epidemiology Group, Human Cancer Genetics Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
Université Paris Sorbonne Cité, UMR-S775 Inserm, Paris, France
Cancer Control Research, BC Cancer Agency, Vancouver, BC, Canada
Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA
College of Pharmacy and Health Sciences, Texas Southern University, Houston, TX, USA
Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
Center for Individualized Medicine, Mayo Clinic, Scottsdale, AZ, USA
Department of Cancer Epidemiology and Prevention, M. Sklodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland
Department of Gynecologic Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA
Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden
National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany
Department of Gynecology, Radboud University Medical Centre, Nijmegen, The Netherlands
Laboratoire de Diagnostic Génétique et Service d’Onco-hématoïgie, Hopitaux Universitaires de Strasbourg, CHRU Nouvel Hôpital Civil, Strasbourg, France
Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA
Anatomical Pathology, The Alfred Hospital, Melbourne, Australia
Institute of Cancer Sciences, University of Glasgow, Wolfson Wohl Cancer Research Centre, Beatson Institute for Cancer Research, Glasgow, UK
Department of Gynecology and Obstetrics, Division of Tumor Genetics, Klinikum rechts der Isar, Technical University Munich, Munich, Germany
Servicio de Anatomía Patológica, Hospital Monte Naranco, Oviedo, Spain
Department of Surgical Gynecology and Gynecological Oncology of Adults and Adolescents, Pomeranian Medical University, Szczecin, Poland
Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
Women's Cancer Research Program, Magee-Women's Research Institute and University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA
Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
Laboratory Medicine Program, University Health Network, Toronto, ON, Canada
Women's College Research Institute, University of Toronto, Toronto, ON, Canada
The University of Texas School of Public Health, Houston, TX, USA
Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, CA, USA
Department of Medicine and Institute for Human Genetics, University of California, San Francisco, CA, USA
Clinical Genetics Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary
Center for Clinical Cancer Genetics and Global Health, University of Chicago Medical Center, Chicago, IL, USA
Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
University of Groningen, University Medical
Center, Department of Genetics, Groningen, The Netherlands  
Department of Molecular Medicine, Sapienza University, Rome, Italy  
Section of Molecular Diagnostics, Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark  
Unit of Medical Genetics, Department of Preventive and Predictive Medicine, Fondazione Istituto di Ricoverye e Cura a Carattere Scientifico Istituto Nazionale Tumori (INT), Milan, Italy  
Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA  
Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia  
Department of Medicine, St Vincent's Hospital, The University of Melbourne, Victoria, Australia  
NRG Oncology Statistics and Data Management Center, Buffalo, NY, USA  
Channing Division of Network Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA, USA  
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  
Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Preventive and Predictive Medicine, Fondazione Istituto di Ricoverye e Cura a Carattere Scientifico, Istituto Nazionale Tumori (INT), Milan, Italy  
Center for Clinical Epidemiology and Biostatistics, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA  
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  
Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT, USA  
NorthShore University Health System, University of Chicago, Evanston, IL, USA  
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  
Department of Gynecology, Jena University Hospital, Jena, Germany  
Ohio State University, Columbus, OH, USA  
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  
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  
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  
Division of Genetics and Epidemiology, The Institute of Cancer Research, Sutton, Surrey, UK  
Institut für Humangenetik Wiesbaden, Wiesbaden, Germany  
Department of Gynecological Oncology, Glasgow Royal Infirmary, Glasgow, UK  
Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Hospices Civils de Lyon, Centre Léon Bérard, Lyon, France  
Department of Clinical Genetics, University and Regional Laboratories, Lund University Hospital, Lund, Sweden  
Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Melbourne, Australia  
Saarland Cancer Registry, Saarbrücken, Germany  
Institut Curie, Department of Tumour Biology, Paris, France
Acknowledgments

We thank all the individuals who took part in this study and all the researchers, clinicians and administrative staff who have made possible the many studies contributing to this work.

The COGS project is funded through a European Commission's Seventh Framework Programme grant (agreement number 223175-HEALTH-F2-2009-223175). The Ovarian Cancer Association Consortium is supported by a grant from the Ovarian Cancer Research Fund thanks to donations by the family and friends of Kathryn Sladek Smith (PPD/ RPCI.07). The scientific development and funding for this project were in part supported by the US National Cancer Institute GAME-ON Post-GWAS Initiative (U19-CA148112). This study made use of data generated by the Wellcome Trust Case Control consortium. A full list of the investigators who contributed to the generation of the data is available from http://www.wtccc.org.uk/. Funding for the project was provided by the Wellcome Trust under award 076113.

G.C.-T. and P.M.W. are supported by the National Health and Medical Research Council; P.A.F. is supported by the Deutsche Krebshilfe; B.K. holds an American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN); K.-A.P. is an Australian National Breast Cancer Foundation Fellow; and A.B. holds the Barbara Thomason Ovarian Cancer Research Professorship from the American Cancer Society (SIOP-06-090-06). R. Balleine was a Cancer Institute NSW Clinical Research Fellow.

OCAC, in particular, acknowledges D. Bowtell, A. deFazio, D. Gertig, A. Green, P. Parsons, N. Hayward and D. Whiteman (AUS); G. Peuteman, T. Van Brussel and D. Sweerts (BEL); U. Eilber and T. Koehler (GER); L. Gacucova (HMO); P. Schirrmann, F. Kramer, W. Zheng, T.-W. Park-Simon, K. Beer-Grondke and D. Schmidt
et al. Page 18

(CIMBA) studies also acknowledge the following. BCFR: This work was supported by grant UM1 CA164920 from the National Cancer Institute. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names and commercial products, or organizations imply endorsement by the US Government or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does

CIMBA: This work was supported by Spanish Association against Cancer (AECC08), RTICC 06/0020/1060, FISI08/1120, Mutua Madrileña Foundation (FMMA) and SAF2010-20493. We thank Alicia Barroso, Rosario Alonso and Guillermo Pita for their assistance. COH: City of Hope Clinical Cancer Genetics Community Network and the Hereditary Cancer Research Registry, supported in part by Award Number RC4CA153828 (PI: J. Weitzel) from the National Cancer Institute and the Office of the Director, National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. CONSIT TEAM: Italian Association for Cancer Research (AIRC) and funds from Italian citizens who allocated the 5 × 1000 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects ‘5 × 1000’). CORE: The CIMBA data management and data analysis were supported by Cancer Research — UK grants C12292/A11174 and C1287/A10118. SH is supported by an NHMRC Program Grant of GCT. ACA is a Cancer Research — UK Senior Cancer Research Fellow. GCT is an NHMRC Senior Principal Research Fellow. DEMOKRITOS: This research has been co-financed by the European Union (European Social Fund — ESF) and Greek national funds through the Operational Program “Education and

CIMBA studies also acknowledge the following. BCFR: This work was supported by grant UM1 CA164920 from the National Cancer Institute. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names and commercial products, or organizations imply endorsement by the US Government or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does

Gynecol Oncol. Author manuscript; available in PMC 2017 May 01.
et al. Page 19

et al. Page 21

Human Genetics Sample Bank. PBCS: This work was supported by the ITT (Istituto Toscano Tumori) grants 2011–2013. SMC: This project was partially funded through a grant by the Israel cancer association and the funding for the Israeli Inherited breast cancer consortium. SMC team wishes to acknowledge the assistance of the Meirav Comprehensive breast cancer center team at the Sheba Medical Center for assistance in this study. SWE-BRCA: SWE-BRCA collaborators are supported by the Swedish Cancer Society. Swedish scientists participating as SWE-BRCA collaborators are: from Lund University and University Hospital: Åke Borg, Hakan Olsson, Helena Jerntström, Karin Henrikssoon, Katja Harbst, Maria Soller, Niklas Loman, Ulf Kristofferson; from Gothenburg Sahlgrenska University Hospital: Anna Öfverholm, Margareta Nordling, Per Karlsson, Zakaria Einbeigi; from Stockholm and Karolinska University Hospital: Anna von Wachenfeldt, Annemie Liljegren, Annika Lindblom, Brita Arver, Gisela Barbany Bustinzia, Johanna Rantal; from Umé University Hospital: Beatrice Melin, Christina Edwindsdotter Ardorn, Monica Emanuelsson; from Uppsala University: Hans Ehrencrona, Maritta Hellström Pigg, Richard Rosenquist; and from Linköping University Hospital: Marie Stemmark-Askmal, Sigrun Liedgren.

UCHICAGO: UCHICAGO is supported by NCI Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA125183), R01 CA142996, U01 CA161032 and by the Ralph and Marion Falk Medical Research Trust, the Entertainment Industry Fund National Women’s Cancer Research Alliance and the Breast Cancer research Foundation. OIO is an ACS Clinical Research Professor. We thank Cecilia Zvocec, Qun Niu, physicians, genetic counselors, research nurses and staff of the Cancer Risk Clinic for their contributions to these resources, and the many families who contribute to our program. UCLA: Patricia Ganz and the Jonsson Comprehensive Cancer Center Foundation; Breast Cancer Research Foundation. We thank Joyce Seldon MSGC and Lorna Kwan, MPH for assembling the data for this study. UCSC: UCSF Cancer Risk Program and Helen Diller Family Comprehensive Cancer Center. We would like to thank Dr. Robert Nussbaum and the following genetic counselors for participant recruitment: Beth Crawford, Kate Loranger, Julie Mak, Nicola Stewart, Robin Lee, Amie Blanco and Peggy Conrad. And thanks to Ms. Salina Chan for her data management. UKFOCR: UKFOCR was supported by a project grant from CRUK to Paul Pharoah. We thank Carole Pye, Patricia Harrington and Eva Wozniak for their contributions towards the UKFOCR. UPENN: National Institutes of Health (NIH) (R01-CA102776 and R01-CA083855); Breast Cancer Research Foundation; Rooney Family Foundation; Susan G. Komen Foundation for the Cure, Bassler Research Center for BRCA. VFTCG: Victorian Cancer Agency, Cancer Australia, National Breast Cancer Foundation. Geoffrey Lindeman, Marion Harris, and Martin Delatycki of the Victorian Familial Cancer Trials Group. We thank Sarah Sawyer and Rebecca Driessen for assembling this data and Ella Thompson for performing all DNA amplification. WCP: The Women's Cancer Program (WCP) at the Samuel Oschin Comprehensive Cancer Institute is funded by the American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN).

BCAC studies also acknowledge the following. We thank all the individuals who took part in these studies and all the researchers, clinicians, technicians and administrative staff who have enabled this work to be carried out. Part of this work was supported by the European Community's Seventh Framework Programme under grant agreement number 223175 (grant number HEALTH-F2-2009-223175) (COGS). This work was partly supported by the Canadian Institutes of Health Research for the “CIHR Team in Familial Risks of Breast Cancer” program (J.S. & D.E.), and the Ministry of Economic Development, Innovation and Export Trade of Quebec — grant # PSR-SIIIRI-701 (J.S. & D.E., P. Hall). The BCAC is funded by CR-UK (C1287/A10118 and C1287/A12014). Meetings of the BCAC have been funded by the European Union COST program (BM0606). D.E. is a Principal Research Fellow of CR-UK. J.S. is chair holder of the Canada Research Chair in Oncogenetics. ABCFS: Maggie Angelakos, Judi Maskill, and Gillian Dite. The ABCFS, NC-BCFR and OFBCR work was supported by the United States National Cancer Institute, National Institutes of Health (NIH) under RFA-CA-06-503 and through cooperative agreements with members of the Breast Cancer Family Registry (BCFR) and Principal Investigators, including Cancer Care Ontario (U01 CA69467), Northern California Cancer Center (U01 CA69417), and University of Melbourne (U01 CA69438). Samples from the NC-BCFR were processed and distributed by the Coriell Institute for Medical Research. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the BCFR, nor does mention of trade names and commercial products, or organizations imply endorsement by the US Government or the BCFR. The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium. J.L.H. is a National Health and Medical Research Council (NHMRC) Australia Fellow and a Victorian Breast Cancer Research Consortium Group Leader. M.C.S. is a NHMRC Senior Research Fellow and a Victorian Breast Cancer Research Consortium Group Leader. The ABCS study was supported by the Dutch Cancer Society [grants NKI 307-08-1889; 2009-4363]; BBMRI-NL, which is a Research Infrastructure financed by the Dutch government (NWO 184.021.007); and the Dutch National Genomics Initiative. BBCC: The work of the BBCC was partly funded by ELAN-Fond of the University Hospital of Erfangen. BBCS: Eileen Williams, Elaine Ryder-Mills, Kara Sargus. The BBCS is funded by Cancer Research UK and Breakthrough Breast Cancer and acknowledges NHS funding to the NIHR Biomedical Research Centre, and the National Cancer Research Network (NCRN). BIGGS: ES is supported by NIHR Comprehensive Biomedical Research Centre, Guy’s & St. Thomas’ NHS Foundation Trust in partnership with King’s College London, United Kingdom. IT is supported by the Oxford Biomedical Research Centre. Niall Mcherney, Gabrielle Colleran, Andrew Rowan, Angela Jones. BSUCH: The BSUCH study was supported by the Dietmar-Hopp Foundation, the Helmholtz Society and the German Cancer Research Center. DKFZ: Research Group Mammkliniker. CECILE: CECILE was funded by Fondation de France, Institut National du Cancer (INCa), Ligue Nationale contre le Cancer, Ligue contre le Cancer.
et al. Page 22

Menendez, the Human Genotyping-CEGEN Unit (CNIO). CTS: The CTS was supported by the California Breast Cancer Act of 1993; National Institutes of Health (grants R01 CA77398 and the Lon V Smith Foundation [LVS39420]); and the California Breast Cancer Research Fund (contract 97-10500). Collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885. ESTHER: The ESTHER study was supported by a grant from the Baden Württemberg Ministry of Science, Research and Arts. Additional cases were recruited in the context of the VERDI study, which was supported by a grant from the German Cancer Aid (Deutsche Krebshilfe). Hartwig Ziegler, Sonja Wolf, Volker Hermann. GENICA: The GENICA was funded by the Federal Ministry of Education and Research (BMBF) Germany grants 01KW9975/5, 01KW9976/8, 01KW9977/0 and 01KW0114, the Robert Bosch Foundation, Stuttgart, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), as well as the Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany. The GENICA Network: Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tübingen, Germany; [H.B., Wing-Yee Lo, Christina Justenhoven], Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany [Yon-Dschun Ko, Christian Baisch], Institute of Pathology, University of Bonn, Bonn, Germany [Hans-Peter Fischer], Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany [U.H.], Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Germany [T.B., Beate Pesch, Sylvia Rabstein, Anne Spickenheuer], Institute of Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Germany [Volker Harth]. HEBCS: The HEBCS was financially supported by the Helsinki University Central Hospital Research Fund, Academy of Finland (132473), the Finnish Cancer Society, The Nordic Cancer Union and the Sigrid Juelius Foundation. Karl von Smitten, Tuomas Heikkinen, Dario Greco, Irja Eirköllä. HMBCS: The HMBCS was supported by a grant from the Friends of Hannover Medical School and by the Rudolf Bartling Foundation. Peter Hillemanns, Hans Christiansen and Johann H. Karstens. HUBCS: The HUBCS was supported by a grant from the German Federal Ministry of Research and Education (RUN08/017). KARBAC: The KARBAC study was supported by the Swedish Cancer Society, the Gustav V Jubilee Foundation and the Bert von Kantzow foundation. KCBP: The KCBP was financially supported by the special Government Funding (EVO) of Kuopio University Hospital grants, Cancer Fund of North Savo, the Finnish Cancer Organizations, the Academy of Finland and by the strategic funding of the University of Eastern Finland. Eija Myöhänen, Helena Kemiläinen. kConFab/AOCS: kConFab is supported by grants from the National Breast Cancer Foundation, the NHMRC, the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia and the Cancer Foundation of Western Australia. The kConFab Clinical Follow Up Study was funded by the NHMRC [145684, 288704, 454508]. Financial support for the AOCS was provided by the United States Army Medical Research and Materiel Command [DAMD17-01-1-0729], Cancer Council Victoria, Queensland Cancer Fund, Cancer Council New South Wales, Cancer Council South Australia, The Cancer Foundation of Western Australia, Cancer Council Tasmania and the National Health and Medical Research Council of Australia [NHMRC; 400413, 400281, 199600]. G.C.T. and P.W. are supported by the NHMRC. Heather Thorne, Eveline Niedermayr, the AOCS Management Group (D Bowtell, G Chenexiv-Trench, A deFazio, D Gertig, A Green, P Webb), the ACS Management Group (A Green, P Parsons, N Hayward, P Webb, D Whiteman). LMBC: LMBC is supported by the ‘Stichting tegen Kanker’ (232-2008 and 196-2010). Diether Lambrechts is supported by the FWO and the KULPFV/10/016-SymBioSysII. Gilian Peuteman, Dominiek Smeets, Thomas Van Brussel and Kathleen Corhouts. MARIE: The MARIE study was supported by the Deutsche Krebshilfe e.V [70-2892-BR I], the Hamburg Cancer German Society, the German Cancer Research Center and the genotype work in part by the Federal Ministry of Education and Research (BMBF) Germany [01KH0402]. Tracy Slangen, Elke Mutschelknauss, Ramona Salazar, S. Behrens, R. Birr, W. Busch, U. Eliber, B. Kaspereit, N. Knese, K. Smit. MBCSG: MBCSG was funded by grants from the Italian Association for Cancer Research (AIRC) and thanks Siranoush Manoukian of the Istituto Nazionale dei Tumori, Milano, Italy; Monica Barile and Irene Feroce of the Istituto Europeo di Oncologia, Milan, Italy; Giuseppe Giannini of the Sapienza University, Rome, Italy; Loris Bernard end per personnel of the Cogentech Genetic Test Laboratory, Milan, Italy. MCBCS: The MCBCS was supported by the NIH grants [CA122340, CA128978], an NIHR Specialized Program Grant [SPG] in Breast Cancer Research Excellence (SPORE) in Breast Cancer Research [CA112611], the Breast Cancer Research Foundation and the Komen Race for the Cure. MCCS: MCCS cohort recruitment in the study was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 209057, 251553 and 504711 and by infrastructure provided by Cancer Council Victoria. MEC: The MEC was support by NIH grants CA63464, CA54281, CA098758 and CA132839. MTLEGBCS: The authors gratefully acknowledge Martine Tranchant for DNA extraction, sample management and skilful technical assistance. J.S. is Chairholder of the Canada Research Chair in Oncogenetics. The work of MTLEGBCS was supported by the Canadian Institutes of Health Research for the “CIHR Team in Familial Risks of Breast Cancer” program — grant # CRN-87521 and the Ministry of Economic Development, Innovation and Export Trade — grant # PSR-SBRI-701. NBCS: The NBCS was supported by grants from the Norwegian Research council, 155218/40, 175240/S10 to ALBD, FUGE-NFR 181600/V11 to VNK and a Swizz Bridge Award to ALBD. NBHS: The NBHS was supported
by NIH grant R01CA100374. Biological sample preparation was conducted the Survey and Biospecimen Shared Resource, which is supported by P30 CA68485. We thank study participants and research staff for their contributions and commitment to this study. NHS: The NHS was funded by NIH grant CA87969. OBBCS: The OBBCS was supported by research grants from the Finnish Cancer Foundation, the Academy of Finland, the University of Oulu, and the Oulu University Hospital. Meerig Otsukka, Kari Mononen. OFBCR: Teresa Sameler, Nayana Weerasooriya. ORIGO: The ORIGO study was supported by the Dutch Cancer Society (RUL 1997-1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16). We thank E. Krol-Warmerdam, and J. Blom for patient accrual, administering questionnaires, and managing clinical information. The LUMC survival data were retrieved from the Leiden hospital-based cancer registry system (ONCODC) with the help of Dr. J. Molenaar. PBCS: The PBCS was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA, Louise Brinton, Mark Sherman, Stephen Chanock, Neunila Szczesnie-Dabrowska, Beata Peplonska, Witold Zatonski, Pei Chao, Michael Stagner. pKARMA: The pKARMA study was supported by Mairit and Hans Rausings Initiative Against Breast Cancer. The Swedish Medical Research Counsel. RBCCS: The RBCCS was funded by the Dutch Cancer Society (DDHK 2004-3124, DDHK 2009-4318). Petra Bos, Jannet Blom, Ellen Crepin, Elisabeth Huijskens, Annette Heemskerk, the Erasmus MC Family Cancer Clinic. SASBAC: The SASBAC study was supported by funding from the Agency for Science, Technology and Research of Singapore (A*STAR), the US National Institute of Health (NIH) and the Susan G. Komen Breast Cancer Foundation. The Swedish Medical Research Counsel. SBCS: The SBCS was supported by Yorkshire Cancer Research S 295, S 299, S 305PA Sue Higham, Helen Cramp, and Dan Connelly. SEARCH: SEARCH is funded by program grants from Cancer Research UK [C490/A11021 and C490/A10124]. The SEARCH and EPIC teams. SKKDKFZS: SKKDKFZS is supported by the DKFZ. We thank all study participants, clinicians, family doctors, researchers and technicians for their contributions and commitment to this study. SZBCS: The SZBCS was supported by Grant PBZ_KBN_122/P05/2004; Katarzyna Jaworska is a fellow of International PhD program, Postgraduate School of Molecular Medicine, Warsaw Medical University, supported by the Polish Foundation of Science. UKBGS: The UKBGS is funded by Breakthrough Breast Cancer and the Institute of Cancer Research (ICR). ICR acknowledges NIHR funding to the NIHR Biomedical Research Centre. We thank Breakthrough Breast Cancer and the Institute of Cancer Research for support and funding of the Breakthrough Generations Study, and the study participants, study staff, and the doctors, nurses and other health care providers and health information sources who have contributed to the study. Genome Quebec: The authors would like to acknowledge the contribution of the staff of the genotyping unit under the supervision of Dr. Sylvie LaBoissière as well as Frédérick Robidoux from the McGill University and Génome Québec Innovation Centre.

References


Fig. 1.
Regional association plots for variants within the genomic region 100 kb either side of KRAS and risk of ovarian and breast cancer. X-axis position is referent to position (bp) on chromosome 12, build GRCh37.p12; yellow line indicates position of KRAS; red triangle indicates rs61764370. Y-axis is $-\log_{10}$(p-values) from association tests for risk of A) ER-negative breast cancer, B) ER-positive breast cancer, C) breast cancer in BRCA1 mutation carriers, D) breast cancer in BRCA2 mutation carriers, E) epithelial ovarian cancer, F) epithelial ovarian cancer in BRCA1 mutation carriers, and G) epithelial ovarian cancer in BRCA2 mutation carriers.
BRCA2 mutation carriers. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Fig. 2.
Power curve for modest risk variants according to the total sample size. X-axis is total sample size for which case-control ratio is 1:1. Y-axis is the statistical power (range 0.5–1.0) for variants given a range of risks, assuming alpha = 0.01 and minor allele frequency 0.09.
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>
<thead>
<tr>
<th></th>
<th>Number Cases</th>
<th>Number Controls</th>
<th>Minor allele frequency Cases</th>
<th>Minor allele frequency Controls</th>
<th>Relative risk (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All invasive</td>
<td>15,357</td>
<td>30,816</td>
<td>0.0914</td>
<td>0.0949</td>
<td>0.99 (0.94–1.04)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade serous</td>
<td>6938</td>
<td>30,816</td>
<td>0.0946</td>
<td>0.0949</td>
<td>1.04 (0.97–1.11)</td>
<td>0.26</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>2151</td>
<td>30,816</td>
<td>0.0834</td>
<td>0.0949</td>
<td>0.90 (0.80–1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Clear cell</td>
<td>1015</td>
<td>30,816</td>
<td>0.0994</td>
<td>0.0949</td>
<td>1.09 (0.94–1.27)</td>
<td>0.27</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1000</td>
<td>30,816</td>
<td>0.0902</td>
<td>0.0949</td>
<td>0.99 (0.85–1.16)</td>
<td>0.91</td>
</tr>
<tr>
<td>Low-grade serous</td>
<td>485</td>
<td>30,816</td>
<td>0.0705</td>
<td>0.0949</td>
<td>0.76 (0.59–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>First-degree family history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>483</td>
<td>342</td>
<td>0.0803</td>
<td>0.0849</td>
<td>0.87 (0.60–1.27)</td>
<td>0.47</td>
</tr>
<tr>
<td>Breast or ovarian cancer</td>
<td>477</td>
<td>18,442</td>
<td>0.0977</td>
<td>0.0915</td>
<td>1.09 (0.93–1.28)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>BRCA1</strong>/<strong>BRCA2</strong> mutation negative</td>
<td>346</td>
<td>15,492</td>
<td>0.1050</td>
<td>0.0997</td>
<td>1.09 (0.85–1.41)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>BRCA1</strong> mutation carriers</td>
<td>2332</td>
<td>12,433</td>
<td>0.0954</td>
<td>0.0922</td>
<td>1.09 (0.97–1.23)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>BRCA2</strong> mutation carriers</td>
<td>599</td>
<td>7305</td>
<td>0.0952</td>
<td>0.0966</td>
<td>0.89 (0.71–1.13)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Enrolled within two years of diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All invasive</td>
<td>10,121</td>
<td>30,815</td>
<td>0.0942</td>
<td>0.0949</td>
<td>0.99 (0.95–1.04)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>BRCA1</strong> mutation carriers</td>
<td>1095</td>
<td>10,802</td>
<td>0.0950</td>
<td>0.0940</td>
<td>1.05 (0.90–1.23)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>BRCA2</strong> mutation carriers</td>
<td>270</td>
<td>6509</td>
<td>0.0907</td>
<td>0.0979</td>
<td>0.85 (0.60–1.20)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Menopausal status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre- or peri-menopausal</td>
<td>4264</td>
<td>8789</td>
<td>0.0915</td>
<td>0.0927</td>
<td>1.02 (0.92–1.13)</td>
<td>0.68</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>11,058</td>
<td>15,903</td>
<td>0.0916</td>
<td>0.0951</td>
<td>0.99 (0.93–1.06)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Gynecol Oncol. Author manuscript; available in PMC 2017 May 01.
<table>
<thead>
<tr>
<th>Enrolled within two years of diagnosis</th>
<th>Cases</th>
<th>Controls</th>
<th>Minor allele frequency</th>
<th>Relative risk (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All invasive</td>
<td>33,530</td>
<td>37,640</td>
<td>0.0904</td>
<td>0.0930</td>
<td>0.98</td>
</tr>
<tr>
<td>Er—/Pr—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Er—/Pr—/Erbb2—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4357</td>
<td>1943</td>
<td>0.0942</td>
<td>0.0954</td>
<td>0.96</td>
</tr>
<tr>
<td>Ovarian or breast cancer</td>
<td>4593</td>
<td>2265</td>
<td>0.0933</td>
<td>0.0949</td>
<td>0.96</td>
</tr>
<tr>
<td>Age diagnosis &lt;52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Er—/Pr—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Er—/Pr—/Erbb2—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brca1/2 mutation negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brca1 mutation carriers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brca2 mutation carriers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolled within two years of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All invasive</td>
<td>20,444</td>
<td>34,349</td>
<td>0.0924</td>
<td>0.0934</td>
<td>0.99</td>
</tr>
<tr>
<td>Brca1 mutation carriers</td>
<td>2595</td>
<td>5976</td>
<td>0.0896</td>
<td>0.0924</td>
<td>0.95</td>
</tr>
<tr>
<td>Brca2 mutation carriers</td>
<td>1359</td>
<td>3365</td>
<td>0.0960</td>
<td>0.0926</td>
<td>1.05</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre- or peri-menopausal</td>
<td>7086</td>
<td>8642</td>
<td>0.0934</td>
<td>0.0933</td>
<td>0.98</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>16,346</td>
<td>18,605</td>
<td>0.0904</td>
<td>0.0943</td>
<td>0.98</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>No. of patients</th>
<th>No. of events</th>
<th>Hazard ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>3096</td>
<td>1421</td>
<td>0.94 (0.83–1.07)</td>
<td>0.38</td>
</tr>
<tr>
<td>Patients who were suboptimally debulked after cytoreductive surgery</td>
<td>1114</td>
<td>784</td>
<td>0.94 (0.78–1.13)</td>
<td>0.50</td>
</tr>
<tr>
<td>Post-menopausal patients &gt; 52 years</td>
<td>2226</td>
<td>1276</td>
<td>0.97 (0.84–1.12)</td>
<td>0.70</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>3096</td>
<td>2144</td>
<td>1.01 (0.90–1.13)</td>
<td>0.84</td>
</tr>
<tr>
<td>Patients who were suboptimally debulked after cytoreductive surgery</td>
<td>1114</td>
<td>961</td>
<td>1.03 (0.87–1.21)</td>
<td>0.74</td>
</tr>
<tr>
<td>Post-menopausal patients &gt; 52 years</td>
<td>2226</td>
<td>1603</td>
<td>1.02 (0.90–1.16)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Breast cancer

| Overall survival |                |               |                       |         |
| All patients | 28,471 | 3013 | 0.96 (0.87–1.06) | 0.38 |
| ER-positive patients | 20,071 | 1754 | 0.96 (0.85–1.10) | 0.58 |
| ER-negative patients | 4778 | 771 | 0.97 (0.81–1.18) | 0.78 |

Breast cancer-specific survival

| Overall survival |                |               |                       |         |
| All patients | 28,471 | 1693 | 0.95 (0.83–1.08) | 0.40 |

| BRCA1 mutation carriers |                |               |                       |         |
| All patients | 1706 | 241 | 0.72 (0.48–1.08) | 0.11 |
| BRCA2 mutation carriers | 917 | 162 | 0.98 (0.65–1.46) | 0.90 |