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Evaluation of a candidate breast cancer associated SNP in *ERCC4* as a risk modifier in *BRCA1* and *BRCA2* mutation carriers. Results from the Consortium of Investigators of Modifiers of *BRCA1/BRCA2* (CIMBA)

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BACKGROUND: In this study we aimed to evaluate the role of a SNP in intron 1 of the *ERCC4* gene (rs744154), previously reported to be associated with a reduced risk of breast cancer in the general population, as a breast cancer risk modifier in *BRCA1* and *BRCA2* mutation carriers.

METHODS: We have genotyped rs744154 in 9408 *BRCA1* and 5632 *BRCA2* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) and assessed its association with breast cancer risk using a retrospective weighted cohort approach.

RESULTS: We found no evidence of association with breast cancer risk for *BRCA1* (per-allele HR: 0.98, 95% CI: 0.93–1.04, $P = 0.5$) or *BRCA2* (per-allele HR: 0.97, 95% CI: 0.89–1.06, $P = 0.5$) mutation carriers.

CONCLUSION: This SNP is not a significant modifier of breast cancer risk for mutation carriers, though weak associations cannot be ruled out.

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Germ-line mutations in the *BRCA1* and *BRCA2* genes confer a high lifetime risk of developing breast and other cancers. Estimates of the cumulative risk of breast cancer to age 70 years vary from 40% to 85% (Easton *et al*, 1995; Ford *et al*, 1998; Antoniou *et al*, 2003; Chen *et al*, 2006; Milne *et al*, 2008). Other genetic and/or environmental factors (modifiers) are likely to explain these differences, at least in part. Because of the large sample size required to identify such effects, few reliable associations have been reported to date, all coming from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) initiative, which was set up to provide large samples of *BRCA1* and *BRCA2* mutation carriers to reliably assess even modest associations with single nucleotide polymorphisms (SNPs) (Chenevix-Trench *et al*, 2007). Recently, CIMBA assessed three SNPs in the *FGFR2*, *TNRC9* and *MAP3K1* genes that had been previously found by a genome-wide association study to be associated with increased breast cancer risk for women in the general population (Easton *et al*, 2007). Consistent associations were found for *BRCA1* and/or *BRCA2* mutation carriers (Antoniou *et al*, 2008), indicating that SNPs involved in the susceptibility to develop breast cancer in the general population are good candidates to be tested as potential modifiers in *BRCA1* and *BRCA2* mutation carriers.

The *ERCC4* gene is involved in the nucleotide excision repair (NER) pathway, which has led to the investigation of its role in the susceptibility to develop different types of cancer including breast cancer (Garcia-Closas *et al*, 2006; Mechanic *et al*, 2006; Moreno *et al*, 2006; Kiyohara and Yoshimasu, 2007; Hooker *et al*, 2008; Smith *et al*, 2008). We previously reported that the minor G allele in a SNP on intron 1 of *ERCC4* (rs744154) was associated with protection from breast cancer in the general population (OR under

a recessive model 0.61; $P = 0.0002$) (Milne *et al*, 2006). On the basis of this finding, we aimed to assess *ERCC4*-rs744154 as a breast cancer risk modifier in *BRCA1* and *BRCA2* mutation carriers. The study was performed in two stages, the first comprising 837 mutation carriers from three CIMBA centres, and the second comprising 15 040 mutation carriers from all the CIMBA studies, including those used in stage I.

MATERIALS AND METHODS

Subjects

Eligible subjects were female carriers of deleterious mutations in *BRCA1* and *BRCA2* aged 18 years or older. Further details regarding eligibility and the information collected from subjects are described elsewhere (Antoniou *et al*, 2008). Subjects who reported having ethnicity other than White European were excluded. This gave a total of 15 040 female mutation carriers (9408 with mutations in *BRCA1* and 5632 with mutations in *BRCA2*), 8088 of whom had been diagnosed with breast cancer (4956 and 3132 with mutations in *BRCA1* and *BRCA2*, respectively). All carriers participated in clinical or research studies at the host institution under ethically approved protocols.

A total of 34 collaborating CIMBA studies, carried out in 18 countries, contributed genotype data for *ERCC4*-rs744154 to this study. Details of each study along with the number of samples included from each are provided in Table 1. Seven studies (CBCS, GOG, ILUH, MSKCC, NNPIO, OSUCCG and IOVHBOCS) had not participated in previous CIMBA collaborations (Antoniou *et al*, 2008). Subjects from the CNIO, HEBCS and MBCSG studies were used in the first stage and comprised 837 mutation carriers (469 in *BRCA1* and 368 in *BRCA2*). All 9408 *BRCA1* and 5632 *BRCA2* mutation carriers CIMBA subjects were included in the second stage.

Genotyping

The genotyping platform used by each study is detailed in Table 1. For 11 studies, matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) was applied to determine allele-specific primer extension products using Sequenom's MassARRAY system and iPLEX technology (Sequenom, San Diego, CA, USA). The design of oligonucleotides was carried out according to the guidelines of Sequenom and performed using MassARRAY Assay Design software (version 3.1). One study determined genotypes by direct sequencing. Genotyping was carried out for the remaining studies by nuclease assay (Taqman). Taqman genotyping reagents were designed by Applied Biosystems (Foster City, CA, USA) (http://www.appliedbiosystems.com/) as Assays-by-Design. Genotyping was performed using the ABI PRISM 7900HT, 7700 or 7500 Sequence Detection Systems according to the manufacturer's instructions. All studies complied with CIMBA genotyping quality control (QC) standards (Antoniou *et al*, 2008).

Table 1 Number of *BRCA1* and *BRCA2* mutation carriers by study

Study	Country of residence	*BRCA1*	*BRCA2*	Genotyping platform
Breast Cancer Family Registry (BCFR)	USA and Australia	492	356	Taqman
Copenhagen Breast Cancer Study (CBCS)	Denmark	92	51	Taqman
CNIO	Spain and Greece[a]	149	198	Taqman
Deutsches Krebsforschungszentrum (DKFZ)	Germany	68	27	Taqman
Hereditary Breast and Ovarian study Netherlands (DNA-HEBON)	The Netherlands	768	293	iPlex[b]
Epidemiological study of BRCA1 and BRCA2 mutation carriers (EMBRACE)	UK and Eire	801	616	iPlex[b]
Fox Chase Cancer Center (FCCC)	USA	82	53	iPlex[b]
German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC)	Germany	799	376	Taqman
Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers (GEMO)	France	1123	565	Taqman
Gynecologic Oncology group (GOG)	USA	391	275	Taqman
Georgetown (GTN)	USA	29	17	iPlex[b]
Hospital Clínico San Carlos (HCSC)	Spain	109	94	Taqman
Helsinki Breast Cancer Study (HEBCS)	Finland	102	104	iPlex[b]
Iceland Landspitali – University Hospital (ILUH)	Iceland		86	Sequencing
Interdisciplinary Health Research International Team Breast Cancer Susceptibility (INHERIT BRCAs)	Quebec-Canada	73	82	Taqman
Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab)	Australia	488	388	iPlex[b]
Mayo Clinic (MAYO)	USA	214	118	iPlex[b]
Milan Breast Cancer Study Group (MBCSG)	Italy	344	218	Taqman
Modifier Study of Quantitative Effects on Disease (ModSQuaD)	Czech Republic	271	128	Taqman
Memorial Sloan-Kettering Cancer Center (MSKCC)	USA	255	157	Taqman
Medical University of Vienna (MUV)	Austria	281	120	iPlex[b]
National Cancer Institute (NCI)	USA	156	73	Taqman
National Israeli Cancer Control Centre (NICCC)	Israel	309	196	Taqman
N.N. Petrov Institute of Oncology (NNPIO)	Russia	66	0	Taqman
Ontario Cancer Genetics Network (OCGN)	Canada	219	170	Taqman
The Ohio State University Clinical Cancer Genetics Program (OSU CCG)	USA	60	31	Taqman
Odense University Hospital (OUH)	Denmark	217	131	Taqman
Istituto Oncologico Veneto (IOVHBOCS)	Italy	93	88	Taqman
Pisa Breast Cancer Study (PBCS)	Italy	72	40	iPlex[b]
Sheba Medical Centre (SMC)-Tel Hashomer	Israel	400	190	Taqman
Swedish Breast Cancer Study (SWE-BRCA)	Sweden	411	120	iPlex[b]
University of Turín Breast Cancer Study (UTBCS)	Italy	61	43	Taqman
University of California Irvine (UCI)	USA	166	120	Taqman
University of Pennsylvania (UPENN)	USA	247	108	iPlex[b]
Total		9408	5632	

[a]The CNIO series consisted of mutation carriers from the Spanish Consortium for the Study of Genetic Modifiers of *BRCA1* and *BRCA2* and the NCSR Demokritos, Athens, Greece. [b]Mutation carriers that failed genotyping are not included in the totals.

Statistical analysis

To test for departure from Hardy–Weinberg equilibrium, a single subject was randomly selected from each family and Pearson's χ^2 Test (1 d.f.) was applied to genotypes from this sample set. The association of *ERCC4*-rs744154 with breast cancer risk was assessed by estimating hazard ratios (HR) and their corresponding 95% confidence intervals (CI) using weighted multivariable Cox proportional hazards regression with robust estimates of variance (Antoniou *et al*, 2005). For each mutation carrier, we modelled the time to diagnosis of breast cancer from birth, censoring at the first of the following events: bilateral prophylactic mastectomy, breast cancer diagnosis, ovarian cancer diagnosis, death and last date known to be alive. Subjects were considered affected if they were censored at breast cancer diagnosis and unaffected otherwise. The weighted cohort approach involves assigning weights separately to affected and unaffected individuals such that the weighted observed incidences in the sample agree with established estimates for mutation carriers (Antoniou *et al*, 2003). This approach has been shown to adjust for the bias in the HR estimates that is a consequence of the ascertainment criteria used (Antoniou *et al*, 2005), which leads to an over-sampling of affected women. Weights were assigned separately for carriers of mutations in *BRCA1* and *BRCA2* and by age interval (<25, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, $\geqslant 70$).

We considered log-additive and codominant genetic models and tested these by applying in the first case a Wald test based on the log-HR estimate per allele and its standard error, and in the second the χ^2 equivalent of a Wald test (on 2 degrees of freedom [d.f.]) based on the log-HR estimates for heterozygotes (CG) and minor-allele-homozygotes (GG) *vs* common homozygotes (CC) and the corresponding variance–covariance matrix. Additional independent variables included in all analyses were year of birth (<1930, 1930–1939, 1940–1949, 1950–1959, 1960–1969, $\geqslant 1970$), study centre and country. Heterogeneity in HRs by study centre was assessed by the χ^2 test described above, but applied to interaction terms for the per-allele effect by centre (on 33 d.f.). A number of sensitivity analyses were applied, including censoring at bilateral prophylactic oophorectomy (BPO), adjusting for BPO (as a time-varying covariate), excluding data used in the initial analysis (from CNIO, HEBCS and MBCSG) and excluding prevalent cases, defined as those diagnosed >3 years before interview or DNA extraction. In addition, an alternative analysis based on a previously described retrospective likelihood approach (Chenevix-Trench *et al*, 2007) was also applied using the pedigree analysis software MENDEL (Lange *et al*, 1988).

All statistical analyses were carried out using Stata: Release 10 (StataCorp. 2007. Stata Statistical Software: Release 10.0. College Station, TX: Stata Corporation LP) unless otherwise stated. Robust estimates of variance were calculated using the *cluster* subcommand, applied to an identifier variable unique to each family.

RESULTS AND DISCUSSION

It is thought that any SNP involved in the susceptibility to develop breast cancer in the general population could also be a phenotypic modifier in carriers of mutations in the high-risk susceptibility genes *BRCA1* and *BRCA2*. This has been confirmed in a recent report from CIMBA in which minor alleles in three SNPs in the *FGFR2*, *TNRC9* and *MAP3K1* genes, previously found to be associated with increased breast cancer risk in the general population (Easton *et al*, 2007), were found to increase breast cancer risk in *BRCA1* and/or *BRCA2* mutation carriers as well (Antoniou *et al*, 2008). We therefore aimed to investigate the role of the rs744154 SNP in *ERCC4* as a potential *BRCA1/BRCA2* risk modifier, based on our earlier finding that the minor G allele was associated with breast cancer protection in the general population (OR under a recessive model 0.61; $P=0.0002$) (Milne *et al*, 2006).

This study was performed in two stages, the first analysing the SNP in 837 carriers of mutations (469 in *BRCA1* and 368 in *BRCA2*) from three CIMBA studies (CNIO, HEBCS and MBCSG). Results of the first stage are summarized in Table 2. We observed a marginally significant association of the G allele in *ERCC4*-rs744154 with breast cancer risk for both *BRCA1* (HR: 0.78, 95% CI: 0.60–1.00, $P=0.05$) and *BRCA2* (HR: 0.68, 95% CI: 0.45–1.02, $P=0.06$) mutation carriers. As this result was consistent with our previously reported protective association in the general population (Milne *et al*, 2006), we genotyped this SNP in subjects from the remaining CIMBA studies and repeated the analysis in the combined series of 9408 *BRCA1* and 5632 *BRCA2* mutation carriers (see Table 2). However, when the whole CIMBA series was analysed (stage II), there was no longer evidence of an association with breast cancer risk for either *BRCA1* (HR: 0.98, 95% CI: 0.93–

Table 2 Genotype frequencies of *ERCC4*-rs744154 by mutation and disease status and hazard ratio estimates from stages I and II

	Genotype	Unaffected (%)	Affected (%)	HR[a]	95% CI	*P*-value
Stage I[a]						
BRCA1 ($n=469$)	CC	104 (50)	148 (57)	1.00		
	CG	85 (41)	96 (37)	0.86	0.62–1.20	
	GG	19 (9)	17 (7)	0.49	0.24–1.01	0.1[b]
	Per allele			0.78	0.60–1.00	0.05
BRCA2 ($n=368$)	CC	73 (45)	109 (53)	1.00		
	CG	81 (49)	82 (40)	0.66	0.40–1.09	
	GG	10 (6)	13 (6)	0.50	0.17–1.47	0.2[b]
	Per allele			0.68	0.45–1.02	0.06
Stage II						
BRCA1 ($n=9408$)	CC	2251 (51)	2603 (53)	1.00		
	CG	1836 (41)	1922 (39)	0.99	0.92–1.07	
	GG	365 (8)	431 (9)	0.96	0.83–1.10	0.8[b]
	Per allele			0.98	0.93–1.04	0.5
BRCA2 ($n=5632$)	CC	1288 (52)	1601 (51)	1.00		
	CG	1012 (40)	1300 (42)	1.05	0.93–1.18	
	GG	200 (8)	231 (7)	0.82	0.65–1.02	0.09[b]
	Per allele			0.97	0.89–1.06	0.5

[a]837 mutation carriers from CNIO, MBCSG and HBCS were included in stage I. Additional mutation carriers from these centres were later genotyped and included in stage II, with carriers from other CIMBA centres. Total number of mutation carriers from these three centres included in the study is provided in Table 1. [b]2-d.f. test.

1.04, $P=0.5$) or *BRCA2* (HR: 0.97, 95% CI: 0.89–1.06, $P=0.5$) mutation carriers. Several sensitivity analyses were performed (see Materials and Methods) but results did not change substantially and so those from the main analysis are presented in this report.

Subsequent to the initiation of this study, a study from the Breast Cancer Association Consortium (BCAC), performed in >30 000 breast cancer cases and 30 000 controls has now found no evidence for an association of rs744154 with breast cancer risk in the general population (Gaudet *et al*, 2009). This is consistent with the lack of association found for *BRCA1* and *BRCA2* mutation carriers. These findings highlight the necessity of very large collaborative efforts to obtain reliable conclusions in genetic association studies. On the basis of the combined results obtained from the BCAC analysis of sporadic breast cancer and the CIMBA analysis of BRCA-related breast cancer – each the largest study of its kind – there no longer seems to be convincing evidence that *ERCC4*-rs744154 is associated with breast cancer risk.

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Conflict of interest

The authors declare no conflict of interest.

REFERENCES

Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjakoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* **72:** 1117 – 1130

Antoniou AC, Goldgar DE, Andrieu N, Chang-Claude J, Brohet R, Rookus MA, Easton DF (2005) A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. *Genet Epidemiol* **29:** 1 – 11

Antoniou AC, Spurdle AB, Sinilnikova OM, Healey S, Pooley KA, Schmutzler RK, Versmold B, Engel C, Meindl A, Arnold N, Hofmann W, Sutter C, Niederacher D, Deissler H, Caldes T, Kampjarvi K, Nevanlinna H, Simard J, Beesley J, Chen X, Neuhausen SL, Rebbeck TR, Wagner T, Lynch HT, Isaacs C, Weitzel J, Ganz PA, Daly MB, Tomlinson G, Olopade OI, Blum JL, Couch FJ, Peterlongo P, Manoukian S, Barile M, Radice P, Szabo CI, Pereira LH, Greene MH, Rennert G, Lejbkowicz F, Barnett-Griness O, Andrulis IL, Ozcelik H, Gerdes AM, Caligo MA, Laitman Y, Kaufman B, Milgrom R, Friedman E, Domchek SM, Nathanson KL, Osorio A, Llort G, Milne RL, Benitez J, Hamann U, Hogervorst FB, Manders P, Ligtenberg MJ, van den Ouweland AM, Peock S, Cook M, Platte R, Evans DG, Eeles R, Pichert G, Chu C, Eccles D, Davidson R, Douglas F, Godwin AK, Barjhoux L, Mazoyer S, Sobol H, Bourdon V, Eisinger F, Chompret A, Capoulade C, Bressac-de Paillerets B, Lenoir GM, Gauthier-Villars M, Houdayer C, Stoppa-Lyonnet D, Chenevix-Trench G, Easton DF (2008) Common breast cancer-predisposition alleles are associated with breast cancer risk in BRCA1 and BRCA2 mutation carriers. *Am J Hum Genet* **82:** 937 – 948

Chen S, Iversen ES, Friebel T, Finkelstein D, Weber BL, Eisen A, Peterson LE, Schildkraut JM, Isaacs C, Peshkin BN, Corio C, Leondaridis L, Tomlinson G, Dutson D, Kerber R, Amos CI, Strong LC, Berry DA, Euhus DM, Parmigiani G (2006) Characterization of BRCA1 and BRCA2 mutations in a large United States sample. *J Clin Oncol* **24:** 863 – 871

Chenevix-Trench G, Milne RL, Antoniou AC, Couch FJ, Easton DF, Goldgar DE (2007) An international initiative to identify genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA). *Breast Cancer Res* **9:** 104

Easton DF, Ford D, Bishop DT (1995) Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Am J Hum Genet* **56:** 265 – 271

Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, Struewing JP, Morrison J, Field H, Luben R, Wareham N, Ahmed S, Healey CS, Bowman R, Meyer KB, Haiman CA, Kolonel LK, Henderson BE, Le Marchand L, Brennan P, Sangrajrang S, Gaborieau V, Odefrey F, Shen CY, Wu PE, Wang HC, Eccles D, Evans DG, Peto J, Fletcher O, Johnson N, Seal S, Stratton MR, Rahman N, Chenevix-Trench G, Bojesen SE, Nordestgaard BG, Axelsson CK, Garcia-Closas M, Brinton L, Chanock S, Lissowska J, Peplonska B, Nevanlinna H, Fagerholm R, Eerola H, Kang D, Yoo KY, Noh DY, Ahn SH, Hunter DJ, Hankinson SE, Cox DG, Hall P, Wedren S, Liu J, Low YL, Bogdanova N, Schurmann P, Dork T, Tollenaar RA, Jacobi CE, Devilee P, Klijn JG, Sigurdson AJ, Doody MM, Alexander BH, Zhang J, Cox A, Brock IW, MacPherson G, Reed MW, Couch FJ, Goode EL, Olson JE, Meijers-Heijboer H, van den Ouweland A, Uitterlinden A, Rivadeneira F, Milne RL, Ribas G, Gonzalez-Neira A, Benitez J, Hopper JL, McCredie M, Southey M, Giles GG, Schroen C, Justenhoven C, Brauch H, Hamann U, Ko YD, Spurdle AB, Beesley J, Chen X, Mannermaa A, Kosma VM, Kataja V, Hartikainen J, Day NE, Cox DR, Ponder BA (2007) Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature* **447:** 1087 – 1093

Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Zelada-Hedman M (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* **62:** 676 – 689

Garcia-Closas M, Malats N, Real FX, Welch R, Kogevinas M, Chatterjee N, Pfeiffer R, Silverman D, Dosemeci M, Tardon A, Serra C, Carrato A, Garcia-Closas R, Castano-Vinyals G, Chanock S, Yeager M, Rothman N (2006) Genetic variation in the nucleotide excision repair pathway and bladder cancer risk. *Cancer Epidemiol Biomarkers Prev* **15:** 536 – 542

Gaudet MM, Milne RL, Cox A, Camp NJ, Goode EL, Humphreys MK, Dunning AM, Morrison J, Giles GG, Severi G, Baglietto L, English DR, Couch FJ, Olson JE, Wang X, Chang-Claude J, Flesch-Janys D, Abbas S, Salazar R, Mannermaa A, Kataja V, Kosma VM, Lindblom A, Margolin S, Heikkinen T, Kampjarvi K, Aaltonen K, Nevanlinna H, Bogdanova N, Coinac I, Schurmann P, Dork T, Bartram CR, Schmutzler RK, Tchatchou S, Burwinkel B, Brauch H, Torres D, Hamann U, Justenhoven C, Ribas G, Arias JI, Benitez J, Bojesen SE, Nordestgaard BG, Flyger HL, Peto J, Fletcher O, Johnson N, Dos Santos Silva I, Fasching PA, Beckmann MW, Strick R, Ekici AB, Broeks A, Schmidt MK, van Leeuwen FE, Van't Veer LJ, Southey MC, Hopper JL, Apicella C, Haiman CA, Henderson BE, Le Marchand L, Kolonel LN, Kristensen V, Grenaker Alnaes G, Hunter DJ, Kraft P, Cox DG, Hankinson SE, Seynaeve C, Vreeswijk MP, Tollenaar RA, Devilee P, Chanock S, Lissowska J, Brinton L, Peplonska B, Czene K, Hall P, Li Y, Liu J, Balasubramanian S, Rafii S, Reed MW, Pooley KA, Conroy D, Baynes C, Kang D, Yoo KY, Noh DY, Ahn SH, Shen CY, Wang HC, Yu JC, Wu PE, Anton-Culver H, Ziogoas A, Egan K, Newcomb P, Titus-Ernstoff L, Trentham Dietz A, Sigurdson AJ, Alexander BH, Bhatti P, Allen-Brady K, Cannon-Albright LA, Wong J, Chenevix-Trench G, Spurdle AB, Beesley J, Pharoah PD, Easton DF, Garcia-Closas M (2009) Five polymorphisms and breast cancer risk: results from the breast cancer association consortium. *Cancer Epidemiol Biomarkers Prev* **18:** 1610 – 1616

Hooker S, Bonilla C, Akereyeni F, Ahaghotu C, Kittles RA (2008) NAT2 and NER genetic variants and sporadic prostate cancer susceptibility in African Americans. *Prostate Cancer Prostatic Dis* **11:** 349 – 356

Kiyohara C, Yoshimasu K (2007) Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: a meta-analysis. *Int J Med Sci* **4:** 59 – 71

Lange K, Weeks D, Boehnke M (1988) Programs for pedigree analysis: MENDEL, FISHER, and dGENE. *Genet Epidemiol* **5:** 471 – 472

Mechanic LE, Millikan RC, Player J, de Cotret AR, Winkel S, Worley K, Heard K, Tse CK, Keku T (2006) Polymorphisms in nucleotide excision repair genes, smoking and breast cancer in African Americans and whites: a population-based case-control study. *Carcinogenesis* **27:** 1377 – 1385

Milne RL, Osorio A, Cajal TR, Vega A, Llort G, de la Hoya M, Diez O, Alonso MC, Lazaro C, Blanco I, Sanchez-de-Abajo A, Caldes T, Blanco A, Grana B, Duran M, Velasco E, Chirivella I, Cardenosa EE, Tejada MI, Beristain E, Miramar MD, Calvo MT, Martinez E, Guillen C, Salazar R, San Roman C, Antoniou AC, Urioste M, Benitez J (2008) The average cumulative risks of breast and ovarian cancer for carriers of mutations in BRCA1 and BRCA2 attending genetic counseling units in Spain. *Clin Cancer Res* **14:** 2861 – 2869

Milne RL, Ribas G, Gonzalez-Neira A, Fagerholm R, Salas A, Gonzalez E, Dopazo J, Nevanlinna H, Robledo M, Benitez J (2006) ERCC4 associated with breast cancer risk: a two-stage case-control study using high-throughput genotyping. *Cancer Res* **66:** 9420 – 9427

Moreno V, Gemignani F, Landi S, Gioia-Patricola L, Chabrier A, Blanco I, Gonzalez S, Guino E, Capella G, Canzian F (2006) Polymorphisms in genes of nucleotide and base excision repair: risk and prognosis of colorectal cancer. *Clin Cancer Res* **12:** 2101 – 2108

Osorio A, Martinez-Delgado B, Pollan M, Cuadros M, Urioste M, Torrenteras C, Melchor L, Diez O, De La Hoya M, Velasco E, Gonzalez-Sarmiento R, Caldes T, Alonso C, Benitez J (2006) A haplotype containing the p53 polymorphisms Ins16bp and Arg72Pro modifies cancer risk in BRCA2 mutation carriers. *Hum Mutat* **27:** 242 – 248

Smith TR, Levine EA, Freimanis RI, Akman SA, Allen GO, Hoang KN, Liu-Mares W, Hu JJ (2008) Polygenic model of DNA repair genetic polymorphisms in human breast cancer risk. *Carcinogenesis* **29:** 2132 – 2138