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7q21-rs6964587 and breast cancer risk: an extended case–control study by the Breast Cancer Association Consortium

Roger L Milne[1], **Justo Lorenzo-Bermejo**[2,3], **Barbara Burwinkel**[4,5], **Núria Malats**[1], **Jose Ignacio Arias**[6], **M Pilar Zamora**[7], **Javier Benítez**[8], **Manjeet K Humphreys**[9], **Montserrat García-Closas**[10,11], **Stephen J Chanock**[10], **Jolanta Lissowska**[12], **Mark E Sherman**[10], **Arto Mannermaa**[13,14], **Vesa Kataja**[15,16], **Veli-Matti Kosma**[13,14], **Heli Nevanlinna**[17], **Tuomas Heikkinen**[17], **Kristiina Aittomäki**[18], **Carl Blomqvist**[19], **Hoda Anton-Culver**[20], **Argyrios Ziogas**[20], **Peter Devilee**[21,22], **Christie J van Asperen**[23], **Rob A E M Tollenaar**[24], **Caroline Seynaeve**[25], **Per Hall**[26], **Kamila Czene**[26], **Jianjun Liu**[27], **Astrid K Irwanto**[27], **Daehee Kang**[28], **Keun-Young Yoo**[28], **Dong-Young Noh**[28], **Fergus J Couch**[29], **Janet E Olson**[30], **Xianshu Wang**[29], **Zachary Fredericksen**[30], **Børge G Nordestgaard**[31,32], **Stig E Bojesen**[31,32], **Henrik Flyger**[33], **Sara Margolin**[34], **Annika Lindblom**[35], **Peter A Fasching**[36,37], **Ruediger Schulz-Wendtland**[38], **Arif B Ekici**[39], **Matthias W Beckmann**[36], **Shan Wang-Gohrke**[40], **Chen-Yang Shen**[41,42], **Jyh-Cherng Yu**[43], **Huan-Ming Hsu**[43], **Pei-Ei Wu**[41,42], **Graham G Giles**[44], **Gianluca Severi**[44], **Laura Baglietto**[44], **Dallas R English**[45], **Angela Cox**[46], **Ian Brock**[46], **Graeme Elliott**[46], **Malcolm W R Reed**[47], **Jonathan Beesley**[48], **Xiaoqing Chen**[48], **kConFab Investigators**[49], **AOCS Group**[48,49], **Olivia Fletcher**[50], **Lorna Gibson**[51], **Isabel dos Santos Silva**[51], **Julian Peto**[51], **Bernd Frank**[4,52], **Joerg Heil**[5], **Alfons Meindl**[53], **Jenny Chang-Claude**[54], **Rebecca Hein**[54], **Alina Vrieling**[54], **Dieter Flesch-Janys**[55,56], **Melissa C Southey**[57], **Letitia Smith**[57], **Carmel Apicella**[45], **John L Hopper**[45], **Alison M Dunning**[58], **Karen A Pooley**[58], **Paul D P Pharoah**[9,58], **Ute Hamann**[59], **Beate Pesch**[60], **Yon-Dschun Ko**[61], **The GENICA Network**[59,60,61,62,63,64], **Douglas F Easton**[9], and **Georgia Chenevix-Trench**[48]

[1]Genetic and Molecular Epidemiology Group, Human Cancer Genetics Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain [2]Institute of Medical Biometry and Informatics, University Hospital Heidelberg, Heidelberg, Germany [3]Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany [4]Molecular Epidemiology Group, DKFZ, Heidelberg, Germany [5]Department of Obstetrics and Gynecology, University Hospital Heidelberg, Heidelberg, Germany [6]Servicio de Cirugía General y Especialidades, Hospital Monte Naranco, Oviedo, Spain [7]Servicio de Oncología Médica, Hospital Universitario La Paz, Madrid, Spain [8]Human Genetics Group, Human Cancer Genetics Program, CNIO, Madrid, Spain [9]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK [10]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA [11]Sections of Epidemiology and Genetics, Institute of Cancer Research and Breakthrough Breast Cancer Research Centre, London, UK [12]Department of Cancer Epidemiology and Prevention, M Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland [13]School of Medicine, Institute of Clinical Medicine, Pathology and

Correspondence to Dr Roger L Milne, Genetic and Molecular Epidemiology Group, Human Cancer Genetics Program, Spanish National Cancer Research Centre (CNIO), Calle Melchor Fernández Almagro, 3, 28039 Madrid, Spain; rmilne@cnio.es.

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Forensic Medicine, University of Eastern Finland, Biocenter Kuopio, Kuopio, Finland [14]Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland [15]Department of Oncology, Kuopio University Hospital, Kuopio, Finland [16]School of Medicine, Institute of Clinical Medicine, Oncology, University of Eastern Finland, Kuopio, Finland [17]Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland [18]Department of Clinical Genetics, Helsinki University Central Hospital, Helsinki, Finland [19]Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland [20]Department of Epidemiology, University of California Irvine, Irvine, California, USA [21]Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands [22]Department of Pathology, Leiden University Medical Centre, Leiden, The Netherlands [23]Department of Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands [24]Department of Surgery, Leiden University Medical Centre, Leiden, The Netherlands [25]Department of Medical Oncology, Rotterdam Family Cancer Clinic, Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam, The Netherlands [26]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden [27]Human Genetics Laboratory, Genome Institute of Singapore, Singapore [28]Seoul National University College of Medicine, Seoul, Korea [29]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA [30]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA [31]Copenhagen General Population Study, Herlev University Hospital, University of Copenhagen, Copenhagen, Denmark [32]Department of Clinical Biochemistry, Herlev University Hospital, University of Copenhagen, Copenhagen, Denmark [33]Department of Breast Surgery (HF), Herlev University Hospital, University of Copenhagen, Copenhagen, Denmark [34]Department of Oncology–Pathology, Karolinska Institute, Stockholm, Sweden [35]Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden [36]Department of Gynecology and Obstetrics, University Breast Center, University Hospital Erlangen, Erlangen, Germany [37]Department of Medicine Division of Hematology and Oncology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA [38]Institute of Diagnostic Radiology, University Hospital Erlangen, Erlangen, Germany [39]Institute of Human Genetics, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany [40]Department of Obstetrics and Gynecology, University of Ulm, Ulm, Germany [41]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan [42]Taiwan Biobank, Taipei, Taiwan [43]Department of Surgery, Tri-Service General Hospital, Taipei, Taiwan [44]Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Australia [45]Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, University of Melbourne, Melbourne, Australia [46]Institute for Cancer Studies, Sheffield University Medical School, Sheffield, UK [47]Academic Unit of Surgical Oncology, Sheffield University Medical School, Sheffield, UK [48]Queensland Institute of Medical Research, Brisbane, Australia [49]Peter MacCallum Cancer Centre, Melbourne, Australia [50]Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, London, UK [51]London School of Hygiene and Tropical Medicine, London, UK [52]Division of Clinical Epidemiology and Aging Research, DKFZ, Heidelberg, Germany [53]Department of Gynaecology and Obstetrics, Technical University of Munich, Munich, Germany [54]Division of Cancer Epidemiology, DKFZ, Heidelberg, Germany [55]Department of Cancer Epidemiology/Clinical Cancer Registry, University Clinic Hamburg-Eppendorf, Hamburg, Germany [56]Institute for Medical Biometrics and Epidemiology, University Clinic Hamburg-Eppendorf, Hamburg, Germany [57]Department of Pathology, The University of Melbourne, Melbourne, Australia [58]Department of Oncology, University of Cambridge, Cambridge, UK [59]Molecular Genetics of Breast Cancer, DKFZ, Heidelberg, Germany [60]Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA), Bochum, Germany [61]Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany [62]Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany [63]University of Tübingen, Tübingen, Germany [64]Institute of Pathology, University of Bonn, Bonn, Germany

Abstract

Background—Using the Breast Cancer Association Consortium, the authors previously reported that the single nucleotide polymorphism 7q21-rs6964587 (*AKAP9*-M463I) is associated with breast cancer risk. The authors have now assessed this association more comprehensively using 16 independent case–control studies.

Methods—The authors genotyped 14 843 invasive case patients and 19 852 control subjects with white European ancestry and 2595 invasive case patients and 2192 control subjects with Asian ancestry. ORs were estimated by logistic regression, adjusted for study. Heterogeneity in ORs was assessed by fitting interaction terms or by subclassifying case patients and applying polytomous logistic regression.

Results—For white European women, the minor T allele of 7q21-rs6964587 was associated with breast cancer risk under a recessive model (OR 1.07, 95% CI 1.00 to 1.13, p = 0.04). Results were inconclusive for Asian women. From a combined analysis of 24 154 case patients and 33 376 control subjects of white European ancestry from the present and previous series, the best-fitting model was recessive, with an estimated OR of 1.08 (95% CI 1.03 to 1.13, p = 0.001). The OR was greater at younger ages (p trend = 0.01).

Conclusion—This may be the first common susceptibility allele for breast cancer to be identified with a recessive mode of inheritance.

INTRODUCTION

In a previous publication, we reported that the M463I variant in the A-kinase anchoring protein 9 gene (*AKAP9*) on chromosome 7 (7q21-rs6964587) was associated with breast cancer risk, based on a study of 9523 patients with breast cancer and 13 770 control subjects from seven independent European and Australian studies.[1] The estimated OR for rare TT homozygotes compared to GG homozygotes was 1.17 (95% CI 1.08 to 1.27, p = 0.0003). We aimed to assess this association more comprehensively by extending the study of this single nucleotide polymorphism to an additional 17 438 female patients with invasive breast cancer and 22 044 female control subjects from 16 independent studies participating in the Breast Cancer Association Consortium, by testing additional genetic models and by considering different breast cancer subtypes defined by immunohistochemical tumour markers.

MATERIALS AND METHODS

Eleven studies were conducted in Europe, two in the USA, one in Australia and two in Asia (table 1). All studies provided information on disease status and ethnic group (white European, Asian, other), as well as age at diagnosis and family history of breast cancer for case patients; all except one (Karolinska Breast Cancer Study) provided age at interview for control subjects. Patients with ‘genetically enriched’ breast cancer were defined as those aged younger than 40 years at diagnosis, with bilateral breast cancer and/or with at least one first-degree relative affected with breast cancer, corresponding to ‘familial’ cases in the original publication.[1] Oestrogen receptor (ER) status and progesterone receptor (PR) status were provided for a subset of 12 385 (77% positive) and 11 347 (63% positive) white European case patients, respectively, while human epidermal growth factor receptor 2 (HER2) status was provided for 5322 (15% positive) white European case patients (table 1). These variables were also obtained for 6228 (77% positive), 5400 (67% positive) and 3614 (18% positive) white European case patients, respectively, from studies that contributed data to the previously published analysis.[1] This histopathology information was generally abstracted from medical reports. Subjects who reported having ethnicity other than white European were excluded, with the exception of those from the two Asian studies (Seoul

Breast Cancer Study and Taiwanese Breast Cancer Study), for which only subjects of Asian origin were included. All subjects gave written informed consent, and each study was approved by relevant local institutional review boards.

The method used by each study to genotype 7q21-rs6964587 is provided in table 1. All studies complied with the Breast Cancer Association Consortium genotyping quality control standards by including at least 2% of samples in duplicate and a common set of 93 CEPH (Centre d'Etude du Polymorphisme Humain) DNAs used by the HapMap Consortium (HAPMAPPT01; Coriell Institute for Medical Research, Camden, New Jersey, USA).

The association of 7q21-rs6964587 with breast cancer risk was assessed by estimating genotype-specific and per-allele ORs using multivariate logistic regression, with study as a categorical covariate. Dominant and recessive models were also considered. Additional adjustment for age made no substantial difference to the results. The best-fitting genetic model was identified using Akaike's Information Criterion (AIC), which is defined as AIC = −2*(ln(likelihood))+2*(number of parameters).[18] Between-study heterogeneity in ORs was assessed using a likelihood ratio test (LRT) comparing the model with interaction terms for the per-allele, dominant or recessive (df = 1), or genotype-specific (df = 2), log-OR by study to the model with no interaction terms. Differences in ORs by ethnicity and age were evaluated using a similar LRT. Differences in ORs between case patient groups defined by ER, PR and HER2 status were tested for white Europeans by an LRT comparing polytomous logistic regression models with and without the per-allele, dominant or recessive (all df = 1) or genotype-specific (df = 2) log-OR constrained to be equal for the two corresponding case patient groups. This LRTwas also used to test the enrichment of the putative risk genotype(s) in *AKAP9*-rs6964587 in selected case patients, even though the OR estimate for genetically enriched case patients cannot be interpreted as a RR.[19] All statistical tests were two-sided. The term 'statistically significant' implies $p<0.05$. All analyses were carried out using Stata: Release 10 (StataCorp).

RESULTS

A minimum genotype concordance of 98% for duplicated samples and 95% for the CEPH samples was observed in all 16 studies, as were minimum genotype calls of 95% for case patients and control subjects. Based on Pearson's χ^2 test applied to control subjects, statistical evidence of departure from Hardy–Weinberg equilibrium was observed for two studies (Genetic Epidemiology Study of Breast Cancer by Age 50 (GESBCS) and Mayo Clinic Breast Cancer Study; p = 0.03 and 0.02, respectively); for both studies, cluster plots were double-checked visually and determined to be of high quality, and all their genotype data were therefore included in the final analysis.

Initial analyses were based on 14 843 case patients and 19 852 control subjects with white European ancestry and 2595 case patients and 2192 control subjects with Asian ancestry. The estimated frequency of the minor (T) allele at 7q21-rs6964587 in control subjects was 0.39 for white Europeans (range among studies 0.37 to 0.42) but lower for Asians (0.17 in both studies) (supplementary table 1). The OR estimate for white Europeans was 1.01 (95% CI 0.98 to 1.04, p = 0.5) per T allele, 0.97 (95% CI 0.92 to 1.02, p = 0.2) for genotype GT versus GG and 1.05 (95% CI 0.98 to 1.12, p = 0.2) for TT versus GG. The corresponding estimates for Asians were 1.07 (95% CI 0.96 to 1.19, p = 0.2), 1.06 (95% CI 0.93 to 1.20, p = 0.4) and 1.16 (95% CI 0.83 to 1.62, p = 0.4), although ORs did not differ by ethnicity ($p>0.4$). In contrast to the previous analysis,[1] there was no evidence of association for white Europeans under a dominant model (OR 0.99, 95% CI 0.94 to 1.03, p = 0.6). However, there was evidence of increased risk under a recessive model (OR 1.07, 95% CI 1.00 to 1.13, p = 0.04). Study-specific OR estimates are provided in figure 1 and in supplementary figure 1.

As observed in the previous publication[1] for the models tested, the recessive OR estimate was greater when case patients with genetically enriched breast cancer were compared to controls (OR 1.13, 95% CI 1.03 to 1.24, p = 0.01). We reanalysed the data from Frank *et al*[1] based on 9311 case patients and 13 524 control subjects of white European ancestry and obtained consistent estimates under the recessive model (OR 1.10, 95% CI 1.02 to 1.19, p = 0.01).

When we combined the data from the 21 studies of white Europeans in the present replication series and those in Frank *et al*[1] (24 154 case patients and 33 376 control subjects in total), we obtained OR estimates of 1.01 (95% CI 0.97 to 1.05, p = 0.6) for genotype GT versus GG and 1.09 (95% CI 1.03 to 1.15, p = 0.002) for TT versus GG. While a log-additive model could not be rejected (per-allele OR 1.04, 95% CI 1.01 to 1.06, p = 0.006, AIC = 74 083.4), the best-fitting model was recessive (AIC = 74 080.6), giving an estimated OR of 1.08 (95% CI 1.03 to 1.13, p = 0.001). The combined recessive OR estimate was higher (OR 1.14, 95% CI 1.06 to 1.22, p = 0.0005), but not statistically significantly so (p = 0.09), when case patients with genetically enriched breast cancer were compared to controls. However, the recessively increased risk was stronger for younger women, with estimated ORs of 1.22 (95% CI 1.02 to 1.45), 1.11 (95% CI 1.03 to 1.19) and 1.01 (95% CI 0.93 to 1.09) for women aged <40, 40–59 and 60 years or older, respectively (p trend = 0.01). There was no evidence of heterogeneity in ORs under any model by study (p≥0.2), and results were consistent across analyses excluding each study, one by one (supplementary table 2), suggesting that no single study was driving them. There was also no evidence of heterogeneity in ORs by tumour ER, PR or HER2 status (p≥0.2) (supplementary table 3).

DISCUSSION

The present study has found independent evidence of an association between 7q21-rs6964587 and breast cancer risk for white women of European origin. This combined analysis of more than 57 000 white European women suggests that homozygotes for the T allele have an average 8% increased risk compared to G allele homozygotes, with no evidence of an increased risk for heterozygotes, and this increased risk was greater for younger women. The results were inconclusive for Asian women, which was not surprising given the smaller sample size and that the Tallele is less frequent; the estimated power to detect a recessive OR of 1.08 at 5% statistical significance was 6%. Given that the replication study was 50% larger than the previous study,[1] that no evidence of log-additive or dominant association was found (p≥0.5) and that the results of the previous study were consistent with the association being recessive, it seems reasonable to assume that the previously reported increased risk for genotype GT versus GG was due to chance.

This may be the first common variant found to be associated with breast cancer risk under a recessive mode of inheritance. However, because T allele homozygotes are relatively uncommon, further large studies will be needed to estimate the associated RR reliably. The 7q21-rs6964587 variant is a potentially deleterious[20] non-synonymous coding single nucleotide polymorphism in *AKAP9*. It is in strong linkage disequilibrium ($r^2 = 0.97$[1]) with 7q21-rs6960867 (*AKAP9*-N2792S), which has also been suggested to be potentially deleterious.[20] However, it is not clear that either variant is causal. They are located in a region of high linkage disequilibrium that spans beyond *AKAP9*, and so the association, if real, may be due to a causal relationship with a variant in another gene nearby. Again, further studies will be required to identify a causal variant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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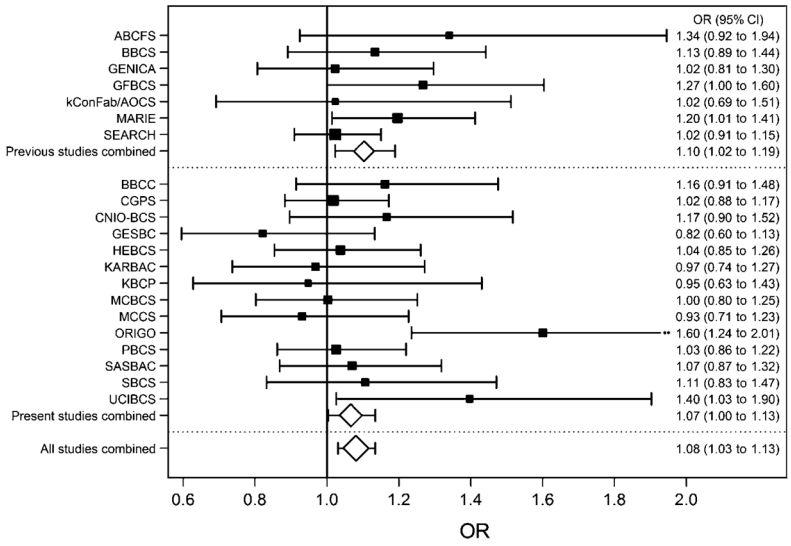

Figure 1.

OR estimates and their associated 95% CIs under a recessive model, by study. The area of the box/diamond is inversely proportional to the standard error of the log-OR estimate.

Table 1

Participating studies, number of subjects and genotyping methods used

Study acronym	Study name (reference)	Country	Controls (n)	Cases (n)	ER	PR	HER2	Genotyping method*
Women of European origin (previously published series)[1]								
ABCFS	Australian Breast Cancer Family Study	Australia	368	540	473 (67)	474 (70)	0	iPLEX
BBCS	British Breast Cancer Study	UK	2635	580	0	0	0	Sentrix
GENICA	Gene Environment Interaction and Breast Cancer in Germany	Germany	995	983	934 (78)	932 (70)	604 (27)	TaqMan
GFBCS	German Familial Breast Cancer Study	Germany	1115	1083	0	0	0	TaqMan
kConFab/AOCS	Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer/Australian Ovarian Cancer Study	Australia	714	271	119 (71)	100 (73)	0	iPLEX
MARIE	Mammary Carcinoma Risk Factor Investigation	Germany	3187	1608	1646 (76)	1644 (64)	1472 (20)	TaqMan
SEARCH	Study of Epidemiology and Risk Factors in Cancer Heredity	UK	4510	4246	3056 (79)	2250 (67)	1538 (11)	TaqMan
Women of European origin (replication series)								
BBCC	Bavarian Breast Cancer Cases and Controls[2]	Germany	965	1251	995 (73)	992 (65)	880 (16)	TaqMan
CGPS	Copenhagen General Population Study[3]	Denmark	6541	1931	1711 (82)	1149 (58)	0	TaqMan
CNIO-BCS	Spanish National Cancer Centre Breast Cancer Study[4]	Spain	807	696	240 (75)	254 (57)	145 (26)	TaqMan
GESBC	Genetic Epidemiology Study of Breast Cancer by Age 50[5]	Germany	560	511	431 (60)	423 (57)	0	TaqMan
HEBCS	Helsinki Breast Cancer Study[6]	Finland	1273	2233	2216 (81)	2215 (65)	1304 (16)	iPLEX
KARBAC	Karolinska Breast Cancer Study[7]	Sweden	855	796	433 (83)	365 (76)	0	TaqMan
KBCP	Kuopio Breast Cancer Project[8]	Finland	404	467	440 (76)	438 (62)	398 (13)	TaqMan
MCBCS	Mayo Clinic Breast Cancer Study[9]	USA	1152	1045	1079 (83)	1074 (73)	735 (20)	TaqMan
MCCS	Melbourne Collaborative Cohort Study[10]	Australia	760	663	605 (73)	606 (57)	396 (12)	TaqMan
ORIGO	Leiden University Medical Centre Breast Cancer Study[11]	Netherlands	1419	552	403 (76)	355 (59)	0	TaqMan
PBCS	NCI Polish Breast Cancer Study[12]	Poland	2323	1941	1808 (65)	1802 (52)	1268 (11)	TaqMan
SASBAC	Singapore and Sweden Breast Cancer Study[13]	Sweden	1458	1217	833 (82)	812 (74)	0	iPLEX
SBCS	Sheffield Breast Cancer Study[14]	UK	822	727	505 (78)	185 (57)	196 (9)	TaqMan
UCIBCS	UCI Breast Cancer Study[15]	USA	513	813	686 (80)	677 (70)	0	TaqMan
Total (white Europeans)			**33 376**	**24 154**	**18 613 (77)**	**16 747 (64)**	**8936 (16)**	
Studies of Asian women (replication series)								

Study acronym	Study name (reference)	Country	Controls (n)	Cases (n)	ER	PR	HER2	Genotyping method*
SEBCS	Seoul Breast Cancer Study[16]	South Korea	1114	1689	0	0	0	TaqMan
TWBCS	Taiwanese Breast Cancer Study[17]	Taiwan	1078	906	779 (63)	779 (56)	347 (33)	TaqMan
Total (Asians)			**2192**	**2595**	**779 (63)**	**779 (56)**	**347 (33)**	

*TaqMan, nuclease assay (TaqMan®), with reagents designed by Applied Biosystems (http://www.appliedbiosystems.com/) as Assays-by-Design^{SM} and genotyping performed using the ABI PRISM 7900HT, 7700 or 7500 Sequence Detection Systems according to manufacturer's instructions; Sentrix, customised Illumina Sentrix Bead Arrays (Illumina, San Diego, California, USA); iPLEX, matrix-assisted laser desorption/ionization time of flight mass spectrometry for the determination of allele-specific primer extension products using Sequenom's MassARRAY system and iPLEX technology (Sequenom, San Diego, California, USA), with oligonucleotide design carried out according to the guidelines of Sequenom and performed using MassARRAY Assay Design software (V.3.1).

ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

ER, number of cases with known ER status (percentage positive in parentheses); PR, number of cases with known PR status (percentage positive in parentheses); HER2, number of cases with known HER2 status (percentage positive in parentheses).