Associations of common variants at 1p11.2 and 14q24.1 *(RAD51L1)* with breast cancer risk and heterogeneity by tumor subtype: findings from the Breast Cancer Association Consortium[†]

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A genome-wide association study (GWAS) identified single-nucleotide polymorphisms (SNPs) at 1p11.2 and 14q24.1 (RAD51L1) as breast cancer susceptibility loci. The initial GWAS suggested stronger effects for both loci for estrogen receptor (ER)-positive tumors. Using data from the Breast Cancer Association Consortium (BCAC), we sought to determine whether risks differ by ER, progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), grade, node status, tumor size, and ductal or lobular morphology. We genotyped rs11249433 at 1p.11.2, and two highly correlated SNPs rs999737 and rs10483813 ($r^2 = 0.98$) at 14q24.1 (RAD51L1), for up to 46 036 invasive breast cancer cases and 46 930 controls from 39 studies. Analyses by tumor characteristics focused on subjects reporting to be white women of European ancestry and were based on 25 458 cases, of which 87% had ER data. The SNP at 1p11.2 showed significantly stronger associations with ER-positive tumors [per-allele odds ratio (OR) for ER-positive tumors was 1.13, 95% CI = 1.10-1.16and, for ER-negative tumors, OR was 1.03, 95% CI = 0.98–1.07, case-only *P*-heterogeneity = 7.6×10^{-5}]. The association with ER-positive tumors was stronger for tumors of lower grade (case-only $P = 6.7 \times 10^{-3}$) and lobular histology (case-only P = 0.01). SNPs at 14g24.1 were associated with risk for most tumor subtypes evaluated, including triple-negative breast cancers, which has not been described previously. Our results underscore the need for large pooling efforts with tumor pathology data to help refine risk estimates for SNP associations with susceptibility to different subtypes of breast cancer.

INTRODUCTION

Genome-wide association studies (GWASs) have successfully identified common single-nucleotide polymorphisms (SNPs) associated with breast cancer risk (1-9). The relative risks associated with these SNPs are small (per allele OR < 1.3), and large samples sizes are necessary to obtain more precise estimates of risk particularly for tumor subtypes. Evaluating the associations between susceptibility loci and tumor subtypes could allow for improved risk assessment; and predicting the risk for specific tumor subtypes may lead to targeted early detection or prevention strategies. A recent multi-stage Cancer Genetic Markers of Susceptibility (CGEMS) GWAS, which included 1145 cases of invasive breast cancer and 1142 controls in the first stage, and 8625 cases and 9657 controls in a replication stage, identified SNPs on 1p11.2 and 14q24.1 to be associated with breast cancer risk (4). Data suggested associations for both SNPs were stronger for estrogen receptor (ER)-positive tumors than for ER-negative tumors, especially for 1p11.2. However, sample sizes in the initial report were limited in being able to detect differences by tumor subtype (4).

The Breast Cancer Association Consortium (BCAC) is an international consortium of breast cancer studies formed to identify and validate genetic risk factors associated with breast cancer (1,9-18). The aim of this study was to more accurately estimate breast cancer risk associated with the 1p.11.2 rs11249433 SNP and two 14q24.1 (*RAD51L1*) highly correlated SNPs (rs999737, rs10483813, $r^2 = 0.98$), and to investigate whether these breast cancer susceptibility SNPs are associated with specific tumor types. Analyses were based on data from a maximum of 39 case-control or cohort studies in BCAC that included 46 036 invasive breast cancer cases and 46 930 unaffected controls.

RESULTS

Study acronyms are defined in Supplementary Material, Table S1, and estimated allele frequencies for each study and P for departure from Hardy-Weinberg equilibrium for the controls are reported in Supplementary Material, Table S2. The frequency of the C-allele for rs11249433 at 1p11.2 ranged between 16 and 26% among white women of European ancestry control groups, and was substantially lower for women of Asian ancestry (2% for Asians versus 23% for Europeans). The frequency of the A-allele for rs10483813 or T-allele for rs999737 at 14q24.1 ranged between 32 and 44% across European ancestry control groups, and was also substantially lower for women of Asian ancestry (3% for Asians versus 40% for Europeans). We estimated per-allele odds ratios (ORs) and 95% confidence intervals (CI) for invasive breast cancer, considering European and Asian women separately, for SNPs at the 1p11.2 and 14q24.1 (RAD51L1) using data from 39 studies (Figs 1 and 2).

Analyses of 1p11.2 SNP rs11249433 and breast cancer risk

Based on the analysis of subjects reporting to be of European ancestry (42 574 invasive cases and 44 467 controls) from 36 studies, the estimated OR per C-allele for rs11249433 was

1.10 (95% CI = 1.08-1.12; $P = 7.2 \times 10^{-17}$, study heterogeneity $I^2 = 14.3$ P = 0.23; Fig. 1). Based on four studies with subjects reporting to be of Asian ancestry (3462 cases and 2463 controls), the estimated per-allele OR was 0.97 (95% CI = 0.79-1.20; P = 0.81; study heterogeneity $I^2 = 0.0$ P = 0.54; Fig. 1). Since the minor alleles for the SNPs analyzed were substantially rarer in Asian populations, we did not observe any significant risk associations in this group, and we had significantly fewer subjects of Asian ancestry, so subsequent analyses were restricted to subjects reporting to be of European ancestry. The estimated ORs for heterozygotes and homozygotes in subjects of European ancestry were: heterozygote OR 1.09 (95% CI = 1.05-1.13; $P = 2.9 \times 10^{-5}$); homozygote OR 1.22 (95% CI = 1.17-1.27; $P = 1.3 \times 10^{-19}$); Supplementary Material, Figure S1.

Using logistic regression models adjusting for study, and data from 1395 DCIS cases and 26 662 controls, there was no evidence for an association between rs11249433 and risk of ductal carcinoma in situ (DCIS): OR 0.98 (95% CI = 0.90 - 1.06; P = 0.57). There was no evidence of differences in OR by age $[1.04 (95\% \text{ CI} = 0.97 - 1.11), 1.10 (95\% \text$ CI = 1.04 - 1.15, 1.11 (95% CI = 1.06 - 1.16), and 1.10 (95% CI = 1.061.14) for age categories <40, 40-49, 50-59and ≥ 60 years, respectively; P = 0.70 for heterogeneity]. Analysis excluding cases selected for family history gave similar estimates to analyses of all invasive cases: per-allele OR 1.11 (95% CI = 1.08 - 1.15). There was also no evidence of differences in the per-allele ORs when case groups were defined by the presence or absence of a firstdegree family member with breast cancer (P = 0.56 for heterogeneity).

Analyses of 14q24.1 (RAD51L1) rs10483813/rs999737 SNPs and breast cancer risk

Based on the analysis of subjects reporting to be of European ancestry from 36 studies, the estimated OR per A-allele for the rs10483813 or T-allele for the rs999737 14q24.1 (RAD51L1) SNPs was 0.92 (95% CI = 0.89-0.94; $\hat{P} = 8.3 \times 10^{-14}$, study heterogeneity $I^2 = 0$, P = 0.76; Fig. 2). The estimated per-allele OR for subjects of Asian ancestry (3459 cases and 2463 controls) from four studies was 1.04 (95% CI = 0.68 - 1.04)1.58; P = 0.87) with some evidence of heterogeneity in OR across studies ($I^2 = 54.1$, P = 0.09; Fig. 2). Since the minor alleles for the SNPs analyzed were substantially rarer in Asian populations, we did not observe any significant risk associations, and we had significantly fewer subjects of Asian ancestry, so subsequent analyses were restricted to subjects reporting to be of European ancestry. The estimated ORs for rs10483813/rs999737 in European women were: heterozygote OR 0.93 (95% CI = 0.90-0.95; $P = 3.54 \times 10^{-7}$); homozygote OR 0.82 (95% CI = 0.77 - 0.88; $P = 6.0 \times$ 10^{-9}); Supplementary Material, Figure S2.

Using data from 1397 DCIS cases and 26 455 controls, the estimated per-allele logistic regression models adjusted for study the OR for DCIS was 0.92 (95% CI = 0.83-1.01; P = 0.08), similar to that for invasive disease. Analysis by age groups did not provide evidence of differences in the OR by age [0.97 (95% CI = 0.90-1.06), 0.90 (95% CI = 0.85-0.95), 0.88 (95% CI = 0.840.92) and 0.96 (95%

White ABCFS ABCS BBCC BBCS BIGGS	1287 1423 930	633		1 02 (0 89 1 17)
ABCFS ABCS BBCC BBCS BIGGS	1287 1423 930	633		1 02 (0 89 1 17)
ABCS BBCC BBCS BIGGS	1423 930	E 40		1.02 (0.03, 1.17)
BBCC BBCS BIGGS	930	546		0.96 (0.84, 1.11)
BBCS BIGGS		932		1.09 (0.96, 1.24)
BIGGS	1151	832	⊥	1.20 (1.06, 1.37)
	907	884		1.04 (0.91, 1.18)
BSUCH	872	837	-	1.12 (0.98, 1.29)
CGPS	2249	6577	- \	1.13 (1.06, 1.21)
CNIO-BCS	711	806		1.10 (0.95, 1.27)
ESTHER	434	517		1.08 (0.90, 1.30)
FBCS	1737	1038		1.04 (0.93, 1.16)
GENICA	1002	1003		1.08 (0.96, 1.23)
GESBC	512	560	- ! •	1.15 (0.97, 1.37)
HABCS	1015	996		1.20 (1.06, 1.36)
HEBCS	2220	1189	-10	1.14 (1.03, 1.27)
HMBCS	1757	1015		0.98 (0.87, 1.09)
HUBCS	723	985		1.07 (0.92, 1.23)
KABBAC	812	859	¥1.	1 12 (0.98, 1.29)
KBCP	475	413		1 14 (0.94, 1.39)
IMBC	1007	1110		1.00 (0.89, 1.13)
MRCSG	274	1000		1.00 (0.83, 1.13)
MCBCSG	1010	1229		1.01 (0.85, 1.21)
MCBCS	1010	1305		1.02 (1.06, 1.14)
MCCS	550	/50		1.23 (1.06, 1.42)
MSKCC	556	474		0.92 (0.77, 1.09)
NC-BCFR-Whites	266	153		1.49 (1.12, 1.99)
OBCS	537	510		1.20 (1.00, 1.44)
OFBCR	1143	326		1.17 (0.98, 1.39)
PBCS	1889	2312		1.14 (1.04, 1.24)
RBCS	706	794		1.11 (0.96, 1.28)
SASBAC	1201	1383		1.12 (1.00, 1.25)
SBCS	886	997		1.00 (0.88, 1.14)
SEARCH	6494	6749	−	1.13 (1.08, 1.19)
SZBCS	710	842	+ <u></u>	1.12 (0.97, 1.29)
UCIBCS	804	506		1.18 (1.01, 1.39)
UKBGS	2341	2341		1.16 (1.07, 1.26)
US3SS	1464	1120		1.04 (0.93, 1.17)
kConFab/AOCS	318	869	++•	1.16 (0.96, 1.39)
Subtotal (I-squared = 14.3	3%, p = 0.230)	◊	1.10 (1.08, 1.12)
Asian				$P = 7.2 \times 10^{-17}$
NC-BCFR-Asians	408	62	•	> 1.36 (0.53, 3.49)
SEBCS	1735	1188	<u>→→→</u>	0.85 (0.64, 1.13)
TBCS	437	295		1.10 (0.66, 1.85)
TWBCS	882	918		1.15 (0.74, 1.77)
Subtotal (I-squared = 0.0°	%, p = 0.544)	10.000		0.97 (0.79, 1.20)
				P = 0.81
Overall (I-squared = 11.99	%, p = 0.259)		6	1.10 (1.07, 1.12)
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Figure 1. Per-allele OR estimates and 95% CIs for 1p11.2 rs11249433 and breast cancer risk by study. Analysis was based on 46 036 invasive breast cancer cases and 46 930 controls from 39 studies. Differences in total numbers are due to missing genotype data. Study acronyms are defined in Supplementary Material, Table S1.

CI = 0.921.00) for age categories <40, 40–49, 50–59, and \geq 60 years, respectively; P = 0.17 for heterogeneity]. Analysis excluding invasive cases selected for family history gave similar estimates to those for all studies: per-allele OR 0.92

(95% CI = 0.88–0.95). There was also no evidence of a difference in the per-allele OR when case groups were defined by first-degree family history of breast cancer (P = 0.24 for heterogeneity).

Study	cases	controls		OR (95% CI)
White			1	
ABCFS	1281	638	- <u>+</u> +	0.99 (0.85, 1.17)
ABCS	1428	547		0.95 (0.81, 1.12)
BBCC	915	946	-+	1.01 (0.87, 1.18)
BBCS	1151	831	-+-	0.93 (0.80, 1.08)
BIGGS	907	887	+	0.95 (0.83, 1.10)
BSUCH	872	832		0.81 (0.69, 0.96)
CGPS	2251	6565	-	0.91 (0.83, 0.98)
CNIO-BCS	716	808	+	0.92 (0.77, 1.09)
ESTHER	436	517		0.93 (0.74, 1.15)
FBCS	1721	1030		0.99 (0.87, 1.13)
GENICA	1013	1007		0.99 (0.85, 1.15)
GESBC	514	559		0.83 (0.68, 1.03)
HABCS	1015	996	_	0.94 (0.81, 1.09)
HEBCS	2208	1265	i	0.79 (0.70, 0.89)
HMBCS	1756	1014	_	0.87 (0.77, 0.99)
HUBCS	723	986		0.94 (0.80, 1.11)
KARBAC	812	862		0.86 (0.73, 1.02)
KBCP	474	411		0.93 (0.73, 1.18)
LMBC	1079	1113	_	0.92 (0.80, 1.06)
MBCSG	274	1231		0.77 (0.60, 0.98)
MCBCS	1019	1364	_	0.90 (0.79, 1.04)
MCCS	654	754		0.96 (0.81, 1.15)
MSKCC	558	473	→ <u></u>	0.88 (0.69, 1.12)
NC-BCFR-Whites	266	154		0.98 (0.70, 1.38)
OBCS	537	510		0.76 (0.61, 0.95)
OFBCR	1142	328	_	0.83 (0.68, 1.03)
PBCS	1910	2333	_ \ _	0.93 (0.84, 1.03)
RBCS	705	791		0.97 (0.82, 1.16)
SASBAC	932	1144	+	0.92 (0.79, 1.07)
SBCS	878	976	<u>_</u>	0.97 (0.83, 1.13)
SEARCH	6482	6743	-	0.91 (0.86, 0.97)
SZBCS	704	857		1.00 (0.85, 1.18)
UCIBCS	810	507	_	0.89 (0.73, 1.07)
UKBGS	2354	2369	-+-	0.93 (0.85, 1.02)
US3SS	1464	1126		0.96 (0.84, 1.09)
kConFab/AOCS	304	814	i	0.72 (0.57, 0.90)
Subtotal (I-squared = 0.0	%, p = 0.761)		0	0.92 (0.89, 0.94)
•				14
Asian				$P = 8.3 \times 10^{-14}$
NC-BCFR-Asians	407	62		1.19 (0.41, 3.42)
SEBCS	1736	1192	!	1.49 (1.08, 2.06)
TBCS	434	293 -	• I I	0.62 (0.29, 1.33)
TWBCS	882	916		0.85 (0.54, 1.36)
Subtotal (I-squared = 54.	1%, p = 0.089	9)		1.04 (0.68, 1.58)
37 55 St				<i>P</i> = 0.87
Overall (I-squared = 0.0%	%, p = 0.482)		6	0.92 (0.90, 0.94)
				and an environment of the state
			I IIII .4 .8 1 1.5 2	

Figure 2. Per-allele OR estimates and 95% CIs for 14q24.1 (*RAD51L1*) rs10483813 or rs999737 and breast cancer risk by study. Analysis was based on 46 036 invasive breast cancer cases and 46 930 controls from 39 studies. Differences in total numbers are due to missing genotype data. Study acronyms are defined in Supplementary Material, Tables S1.

Analyses of 1p11.2 SNP rs11249433 and 14q24.1 (RAD51L1) rs10483813/rs999737 SNPs by ER, PR and HER2 status of tumors

The majority of studies (26 of 36 studies with women reporting to be of European ancestry) contributed information on the pathology of the breast tumor, and analyses were based on up to 35 209 controls and 25 458 cases. The 1p11.2–rs11249433 SNP exhibited a stronger association with ER-positive tumors than that with ER-negative tumors (Table 1). Per-allele ORs for ER-positive and ER-negative tumors were 1.13 (95% CI = 1.10-1.16) and 1.03 (95% CI = 0.981.07), respectively

Table 1.	Per-allele OR and 95% CIs for the association of SNPs at 1p11.2 rs11249433 and 14q24.1 (RAD51L1) rs10483813 or rs999737	and breast cancer risk by
ER, PR a	and HER2 tumor expression for cases and controls reporting European Caucasian ancestry	

Locus	SNP	Case-co	ntrol									Case-only P
		п	OR	95% C	ľ	Р	п	OR	95% C	I	Р	5
		ER+ tur	nors vers	us contro	ls		ER-t	umors ve	ersus cont	rols		
1p11.2	rs11249433	16 874	1.13	1.10	1.16	3.71E-18	5099	1.03	0.98	1.07	0.21	7.6 E-05
14q24.1	rs10483813 or rs999737	16 693	0.90	0.87	0.93	1.32E-09	5060	0.93	0.88	0.98	0.004	0.42
		PR+ tur	nors vers	us contro	ls		PR-t	umors ve	rsus cont	rols		
1p11.2	rs11249433	12 708	1.13	1.10	1.17	7.55E-16	6624	1.07	1.03	1.11	0.001	0.007
14q24.1	rs10483813 or rs999737	12 545	0.91	0.88	0.95	7.28E-07	6582	0.90	0.86	0.94	0.00001	0.42
		HER2-	tumors v	ersus cor	ntrols		HER2-	+ tumors	versus co	ontrols		
1p11.2	rs11249433	7138	1.11	1.06	1.15	8.36E-07	1964	1.06	0.99	1.13	0.09	0.231
14q24.1	rs10483813 or rs999737	7137	0.91	0.86	0.95	5.84E-05	1956	0.85	0.78	0.92	1.04E-04	0.077

Analysis included a maximum of 35 209 controls and 22 116 cases with genotypes and ER status (cases-only); 35 210 controls and 19 471 cases for PR analysis; 28 194 controls and 9 178 cases for HER2. Differences in total number are due to missing genotype data. ORs are adjusted by study and are for European Caucasians only. Case-only *P*-value was used to test for heterogeneity, and was estimated using a polytomous logistic regression model with receptor status as the outcome adjusted by study.

Table 2. Per-allele ORs and 95% CIs for the association of SNPs at 1p11.2-rs11249433 and 14q24.1 (RAD51L1) rs10483813 or rs999737 and breast cancer risk by ER. PR and HER2 expression in tumors for cases and controls reporting European Caucasian ancestry

Locus	SNP	Case-c n	ontrol OR	95% C	I	Р	n	OR	95% C	I	Р	Case-only <i>F</i>
		ER+/P	R+ and I	HER2-				ER+/I	PR+ and	HER2+		
1p11.2	rs11249433	5834	1.10	1.06	1.15	4.58E-06	1296	1.09	1.00	1.18	0.037	0.80
14q24.1	rs10483813 or rs999737	5828	0.92	0.88	0.97	0.002	1296	0.82	0.74	0.90	0.0001	0.02
1		Triple-1	negative t	umors				ER-,	PR- and	HER2+		
1p11.2	rs11249433	1155	1.07	0.98	1.17	0.11	635	1.02	0.91	1.14	0.71	0.49
14q24.1	rs10483813 or rs999737	1160	0.89	0.80	0.98	0.02	627	0.93	0.82	1.07	0.30	0.56

Analysis included a maximum of 28 194 controls and 8997 cases. ORs are adjusted by study and are for European Caucasians only. Case-only *P*-value was used to test for heterogeneity, and was estimated using a polytomous logistic regression model comparing ER+/PR+ and HER2+ versus ER+/PR+ and HER2-tumors and triple-negative versus ER-/PR- and HER2+ tumors, respectively. Differences in total number are due to missing genotype data.

(case-only *P*-heterogeneity = 7.6×10^{-5}). In contrast, for rs10483813/rs999737, there was an association with both ER-positive and ER-negative disease, with per-allele OR of 0.90 (95% CI = 0.87 - 0.93) for ER-positive and 0.93(95% CI = 0.88 - 0.98) for ER-negative tumors (case-only *P*-heterogeneity = 0.42). Analyses by PR status for the 1p11.2 and 14q24.1 (RAD51L1) SNPs showed similar results to those observed by ER status (Table 1). The estimated OR for rs11249433 was slightly higher for HER2-negative than that for HER2-positive disease (case-only *P*-heterogeneity = 0.23, Table 1), but no difference by HER2 status was observed when ER/PR-positive and ER/PR-negative cases were considered separately (case-only *P*-heterogeneity = 0.80 and 0.49, respectively; Table 2). There was a slight suggestion of stronger effects for the rs10483813/rs999737 SNP and HER2-positive tumors with per-allele OR of 0.91 (95% CI = 0.86 - 0.95) for HER2-negative and 0.85 (95%) CI = 0.78 - 0.92) for HER2-positive tumors (case-only P-heterogeneity = 0.08, Table 1). There was still some suggestion of a difference by HER2 status among ER/PR-positive tumors (case-only *P*-heterogeneity = 0.02, Table 2); however, there was no suggestion of differences among ER/PR-negative cases by HER2 expression (case-only *P*-heterogeneity = 0.56, Table 2).

Analyses of 1p11.2 SNP rs11249433 and 14q24.1 (RAD51L1) rs10483813/rs999737 SNPs by other tumor characteristics

The 1p11.2 rs11249433 SNP showed a stronger association with tumors of lower grade ($P = 7 \times 10^{-6}$; Table 3). There was some indication of a higher risk for low-grade rather than higher grade ER-positive tumors (adjusted case-only $P = 6.7 \times 10^{-3}$; Table 3), and no association with ER-negative tumors of any grade (adjusted case-only P = 0.99; Table 3). There was no difference in risk by grade for the rs10483813/rs999737 14q24.1 (*RAD51L1*) SNPs (Table 3). There was evidence of a higher risk for ER-positive tumors of lobular compared with ductal tumors for rs11249433 (1p11.2) (P = 0.01; Table 3), but no evidence for such differences in risk for rs10483813/rs999737 (P = 0.81; Table 3). We found no evidence of heterogeneity for risk associated with 1p11.2 SNP rs11249433 and 14q24.1 (*RAD51L1*) rs10483813/rs999737 SNPs by node status or tumor size (Tables 4 and 5).

DISCUSSION

Our large study has confirmed the associations with breast cancer risk for both rs11249433 SNP at 1p11.2 and

Locus	SNP	Cases (g	(rade)		Grade	1		Grade	2		Grade	3		Case-only
		1	2	3	OR	95% (CI	OR	95% (CI	OR	95% (CI	P
All tumors														
1p11.2	rs11249433	5222	10952	7471	1.18	1.13	1.23	1.12	1.09	1.16	1.05	1.01	1.09	7.01E-06
14q24.1	rs10483813 or rs999737	5193	10851	7301	0.88	0.84	0.93	0.93	0.9	0.97	0.91	0.87	0.95	0.51
ER-positiv	e tumors only													
1p11.2	rs11249433	3697	7307	3204	1.18	1.13	1.25	1.13	1.09	1.17	1.08	1.02	1.14	6.67E-03
14q24.1	rs10483813 or rs999737	3680	7244	3111	0.87	0.82	0.92	0.92	0.88	0.96	0.89	0.83	0.95	0.50
ER-negativ	e tumors only													
1p11.2	rs11249433	286	1120	2618	1.01	0.85	1.2	1.03	0.94	1.12	1.01	0.95	1.07	0.99
14q24.1	rs10483813 or rs999737	285	1116	2588	1.06	0.87	1.29	0.92	0.83	1.02	0.89	0.83	0.96	0.19
		Cases (h	istology)		Ducta	1		Lobul	ar		Other			Ductal/lobula
Locus	SNP	Ductal	Lobular	Other	OR	95% (CI	OR	95% (CI	OR	95% (CI	Р
All tumors														
1p11.2	rs11249433	19 197	3742	2381	1.10	1.07	1.13	1.21	1.16	1.28	1.11	1.04	1.18	0.0001
14q24.1	rs10483813 or rs999737	18 940	3709	2361	0.91	0.88	0.94	0.91	0.85	0.96	0.92	0.86	0.99	0.81
ER-positiv	e tumors only													
1p11.2	rs11249433	10 558	2460	972	1.12	1.09	1.16	1.22	1.15	1.29	1.09	1.00	1.20	0.01
14q24.1	rs10483813 or rs999737	10 398	2443	962	0.91	0.88	0.95	0.89	0.83	0.95	0.90	0.81	1.01	0.56
ER-negativ	e tumors only													
1p11.2	rs11249433	3544	296	399	1.01	0.96	1.07	1.16	0.99	1.37	1.04	0.90	1.20	0.15
14q24.1	rs10483813 or rs999737	3516	292	395	0.93	0.88	0.99	0.85	0.70	1.04	0.93	0.78	1.10	0.27

Table 3. Per-allele ORs and 95% CI for the association of SNPs at 1p11.2-rs112494331p11.2 rs11249433 and 14q24.1 (RAD51L1) rs10483813 or rs999737 and breast cancer risk by tumor grade and histology stratified by ER tumor expression

Analysis included a maximum of 35 082 controls and max. 23 800 cases with genotypes, and grade status (cases only); and 33 535 controls and max. 25 458 cases with genotypes, and histopathology information (cases only). ORs are adjusted by study and are for European Caucasians only. Case-only *P*-value was used to test for heterogeneity, and was estimated using a polytomous logistic regression model with ductal histology as the referent.

Table 4. Per-allele ORs and 95% CIs for the association of SNPs at 1p11.2 rs11249433 and 14q24.1 (RAD51L1) rs10483813 or rs999737 and breast cancer risk by node status

Locus	SNP	Case-control Node-positive t	umors v	ersus controls		Node-negative	tumors	versus controls		Case-only P
		Node $+$ cases	OR	95% CI	Р	Node – cases	OR	95% CI	Р	
1p11.2 14q24.1	rs11249433 rs10483813 or rs999737	8868 8798	1.11 0.90	1.05 - 1.16 0.87 - 0.93	1.05E-04 1.32E-09	13,747 13,520	1.11 0.94	1.07 - 1.16 0.89 - 0.98	1.8 E-07 0.01	0.80 0.53

Analysis included a maximum of 33 284 controls and max 22 755 cases with genotypes, and node information (cases-only). ORs are adjusted by study and are for European Caucasians only. Case-only *P*-value was used to test for heterogeneity, and was estimated using a polytomous logistic regression model with node-positive status as the referent.

rs10483813/rs999737 at 14q24.1 and refined the risk estimates by clinically important tumor characteristics. The estimated ORs for rs11249433 for women of European ancestry were lower than reported by Thomas *et al.* (4) (Thomas *et al.* reported heterozygote OR = 1.16 versus BCAC OR = 1.09; and homozygote OR = 1.30 versus BCAC OR = 1.22). The estimated homozygote OR for rs10483813/rs999737 was also attenuated toward null in this study (Thomas *et al.* reported heterozygote OR = 0.94 versus BCAC OR = 0.93; and homozygote OR = 0.70 versus BCAC OR = 0.82). This attenuation may reflect an overestimation in the initial GWAS reports due to 'winner's curse'.

In addition to the estimates of association for European women, we also estimated risks for Asian women based on 3462 cases and 2463 controls from four studies. Neither locus showed evidence for an association in this group, but the estimated per-allele ORs for Asians were both consistent with that reported for Europeans. The wide confidence intervals in Asians were due to the smaller sample size but also the low minor allele frequencies in (both MAF < 3%). Future studies involving larger numbers of subjects of other race/ethnicities will be necessary to clarify the issue of consistency of findings across racial/ethnic groups.

For the 1p11.2 rs11249433 SNP, we found evidence for a greater OR for ER-positive versus ER-negative disease, consistent with the initial report (4). Thomas *et al.* reported a P value of 0.001 for heterogeneity from case-only analysis for this same SNP. This observation was based on 6586 cases, 1314 of which were ER-negative in the initial GWAS report. We investigated the association of these SNPs and ER expression based on 22 116 cases; of which, 5099 were ER-negative and found little evidence of any association with ER-negative disease. Our data showed that the 1p11.2 locus was most strongly associated with ER-positive tumors that are of low grade and lobular histology, which are more likely to be screen-detected and tend to have good prognosis. In contrast, rs10483813/rs999737 was associated with

Loomo	END	Case (F	(onio some		0	1 2000			0	1 2 200			0				
rocus	INC	≤lcm	> 1-2 cm	$>2\mathrm{cm}$	OR	95% C	Ι	Ρ	OR	95% CI		Ρ	OR	95% CI		Ρ	Case-only r
1p11.2	rs11249433	3910	8716	7448	1.14	1.09	1.20	1.16E - 07	1.09	1.05	1.13	2.81E-06	1.12	1.07	1.16	1.02E - 08	0.72
14q24.1	rs10483813 or rs999737	3807	8581	7375	0.95	0.90	1.01	0.08	0.90	0.86	0.94	1.33 E - 06	0.91	0.87	0.95	3.18E - 05	0.49

Analysis included max. 30 771 controls and max. 20 193 cases with genotypes, and turnor size information (cases-only). ORs are adjusted by study and are for European Caucasians only. Case-only P-value

was used to test for heterogeneity, and was estimated using a polytomous logistic regression models constraining the effect size to increase linearly across levels

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multiple tumor types, and showed little evidence for a difference in OR by tumor characteristics except for potentially HER2 expression. In particular, the SNP showed clear evidence for an association with both ER-positive and ER-negative disease and refutes the initial finding reported by Thomas et al. Our results by ER status are also consistent with parallel findings assessing modification of risk in BRCA1/ 2 carriers by The Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), which show that rs11249433 modifies risk of BRCA2 carriers but rs10483813/rs999737 has no apparent association with risk on the background of familial risk conferred by BRCA1 or BRCA2 mutations (19). Further, our estimates for risk of DCIS suggested similar effects to invasive disease for the14q24.1 region, which we did not observe for the 1p11.2 region. Together, these data do not support the previous report that the 14q24.1 rs10483813/rs999737 SNP associations are stronger for ER-positive breast cancer (4), and rather our data indicate that this locus confers susceptibility to various subtypes of breast cancer.

The rs11249433 SNP locus is located in a relatively large nongenic region of high linkage disequilibrium (LD) very close to the centromere of chromosome 1, a region notoriously difficult to map. The closest neighboring genes to this SNP are genes in the low-affinity Fc gamma receptor family, *FCGR1B*, and the transmembrane protein coding gene *NOTCH2*. SNPs in this region have recently been associated with type 2 diabetes (20). Recent pooled analysis have shown diabetes and related conditions to increase risk of death for breast cancer (21); however, epidemiological studies of type 2 diabetes and breast cancer risk have given mixed results (22–24). A recent study found some evidence of increased *NOTCH2* expression in breast tumors in carriers of the C allele of rs11249433, suggesting that the breast cancer susceptibility at this locus may be mediated through variation in *NOTCH2* expression (25).

Both rs999737 and rs10483813 lie within an LD block in intron 10 of *RAD51L1* (also known as *RAD51B*). *RAD51L1* is a member of the Rad51-like proteins that are involved in doublestrand break (DSB) repair and homologous recombination (26). Rare mutations in other genes in this pathway (notably *BRCA1* and *BRCA2*) predispose to high risks of breast cancer, and most recently common susceptibility variants in another DSB repair genes (near *MERIT40* on chromosome 19p13) have been shown to modify risk for *BRCA1* mutation carriers (27). Assuming that the risk association is mediated through an effect on RAD51L1 expression/function, the identification and confirmation of the 14q24.1 (*RAD51L1*) locus increases the number of genes within the repair pathway that may be important for susceptibility to breast and other cancers.

The analyses presented here have resulted in refined relative risk estimates on the largest sample size to date for overall breast cancer risk and risk for specific tumor subtypes, a very important consideration for low-risk alleles of modest effect that will, in the future, be used together in risk models to assess the likelihood that women will be predisposed to breast cancer. Our analyses of these two loci highlight the notion that some susceptibility factors are more strongly associated with specific subtypes (e.g. 1p11.2 SNPs are more strongly associated with ER-positive tumors of low grade and lobular histology), while other loci are associated across different subtypes of breast cancer (e.g. 14q24.1). These findings demonstrate the importance of conducting large studies with tumor pathology data in order to refine risk estimates for all risk-associated SNPs identified by GWAS and other studies, to provide the most robust SNP risk models possible for assessing predisposition to different types of breast cancer.

Key strengths of our study are its large sample size, and data on tumor characteristics. Our study had >80% power at P < 0.05 to detect an OR of 1.1 for ER and PR subtype analysis and 70% power for the rarer HER2+ breast cancers. A limitation is the use of non-standardized data on tumor markers since data were derived from studies using different tissue collection and processing protocols, immunohistochemical assays, and criteria for pathology review. Nevertheless, we observed consistent associations across studies, indicating that our findings are robust and highlight that breast tumors are etiologically distinct. Further genetic mapping and functional analyses will be required to determine the genetic variants underlying both these susceptibility loci signals, and to delineate the biological pathways involved in susceptibility to different subtypes of breast cancer.

MATERIALS AND METHODS

Study samples

Thirty-nine breast cancer studies participating in BCAC contributed data for cases and controls for the 1p11.2 SNP rs11249433, and at least one of the two highly correlated SNPs rs10483813 or rs999737 at14q24.1 (RAD51L1) (see Supplementary Material, Table S1 for a list of studies and abbreviations, and a more detailed description of participating studies). After excluding subjects that did not report to be of European or Asian ancestry, the number of subjects available for analysis was 46 036 invasive breast cancer cases, and 46 930 controls from case-control or prospective cohort studies. Data on age and race/ethnicity of participants was provided by each study. Primary analysis estimated per-allele OR for Europeans and Asian separately. Thirty-six studies from Europe, North America and Australia included predominantly women of white European ancestry. Except for the NC-BCFR study, women whose reported race/ethnicity was non-European were excluded from analyses. The NC-BCFR study had >100 subjects reporting European or Asian ancestry, and was separated into two groups for analysis: NC-BCFR whites and NC-BCFR Asians. Analyses of Asian women included four studies, one each from the USA (NC-BCFR Asians), Korea (SEBCS), Taiwan (TWBCS) and Thailand (TBCS). We also had data on 1397 cases with ductal carcinoma in situ (DCIS) from 24 studies from women of European descent.

Pathology and tumor markers

The final numbers available for analysis were 46 036 invasive breast cancer cases and 46 930 controls from 39 studies and pathology data included in each analysis are shown in Tables 1-5. Of the 36 studies that reported women of European ancestry, the majority provided information on histopathologic subtype (24 studies: 76% ductal, 15% lobular, 9% other histologies), grade of differentiation (25 studies;

22% grade 1, 46% grade 2 and 32% grade 3 or higher), tumor size (21 studies: 19% with the size of 1 cm or less, 43% with the size of >1-2 cm and 37% with the size of >2 cm) and nodal involvement (26 studies: 60% node positive). Twenty-six studies provided data on ER and PR status and 18 on HER2 status.

Genotyping

Genotyping for three SNPs (rs11249433, rs10483813 and rs999737) was performed in the framework of BCAC as described previously (10–13,15). Most studies carried out genotyping using Taqman nuclease assay (Taqman[®]), with reagents designed by Applied Biosystems (http://www.app liedbiosystems.com/) as Assays-by-DesignTM and genotyping performed using the ABI PRISM 7900HT, 7700 or 7500 Sequence Detection Systems according to manufacturer's instructions. A few studies (GENICA, HEBCS, kConFab/AOCS, LMBC, MBCSG and SASBAC) used the Sequenom iPLEX MassARRAYTM system (Sequenom, San Diego, CA, USA) with oligonucleotide design performed using MassARRAY Assay Design software (version 3.1). Genotyping platform used by each study are indicated in Supplementary Material, Table S2.

Out of 40 studies that performed the genotyping, data from only one study were excluded due to not meeting the BCAC quality control (QC) guidelines: (i) individual samples were excluded based on the number of SNPs that were typed in this phase of genotyping by each study, which were three SNPs (rs11249433, rs10483813/rs999737 and rs2046210). Any given sample was excluded if it failed genotyping for two of the three SNPs. (ii) All samples on any one plate were excluded if the plate had a SNP call rate <90%; (iii) all genotype data for any SNP were excluded if the overall call rate was <95%; or data for any SNP where duplicate concordance was <98%. For any SNP for which the P-value for departure from Hardy-Weinberg equilibrium for controls was < 0.005, clustering of the intensity plots was reviewed manually by a single person and clustering was judged to be fine. In addition, all genotyping centers assayed an identical plate of 94 control CEPH DNA samples referred to as the Coriell plate (HAPMAPPT01, Coriell Institute for Medical Research, Cambden, NJ, USA); which also included five internal duplicates. Studies had to achieve a call rate >90% and concordance >98% in order for their data to be included. After applying these QC guidelines, data were available for a total of 39 studies (see Supplementary Material, Table S1). For the 14q24.1 SNP data, 33 studies genotyped rs10483813, and five studies (GENICA, HEBCS, LMBC, SASBAC and KCONFAB-AOCS) genotyped rs999737. One study from Italy (MBCSG) genotyped both SNPs ($r^2 = 0.98$, based on 1217 control samples, Supplementary Material, Table S3). For the MBCSG study, data for rs10483813 were used in the analysis.

Statistical analysis

Departure from Hardy–Weinberg equilibrium was tested for controls from each center using Pearson's χ^2 -test with 1*df*. We presented the association of each SNP with breast cancer risk assessed by meta-analysis using genotype

frequencies in cases and controls. We also performed multiple logistic regression adjusted for study which gave similar results to meta-analysis (data not shown). For each SNP, we performed one analysis estimating the separate odds ratios (ORs) and 95% confidence intervals (CIs) for heterozygotes and homozygote variants relative to the common-allele homozygotes, and another analysis assuming a log-additive model to estimate the OR per variant allele, assuming a log-additive model. Between-study heterogeneity in OR was expressed using the I^2 statistic. Polytomous logistic regression was used to estimate the OR for each breast cancer subtype (comparing case subtypes with all controls). OR and 95% CI were estimated assuming a log-additive model for the association with genotype, adjusted by study. Heterogeneity between genotype OR for different tumor subtypes was assessed using logistic regression analyses restricted to cases (case-only analyses) with the tumor characteristic as the outcome variable. For tumor subtypes with more than two levels (i.e. grade and size), we used a polytomous logistic regression model constraining the strength of association to increase linearly across levels (e.g. the parameter for grade 3 versus grade 1 was constrained to be twice that for grade 2 versus grade 1). All statistical tests were two-sided. To test if the per-allele ORs differed by age or family history, a likelihood ratio test was used from fitting logistic regression models with and without interaction terms. All analyses were carried out using Stata: Release 9 (College Station, TX, USA).

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG online.

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APPENDIX

The list of study abbreviations

ABCFS: Australian Breast Cancer Family Study; ABCS: Amsterdam Breast Cancer Study; BBCC: Bavarian Breast Cancer Cases and Controls; BBCS: British Breast Cancer Study; BIGGS: Breast Cancer in Galway Genetic Study; BSUCH: Breast Cancer Study of the University of Heidelberg; CGPS: Copenhagen General Population Study; CNIO-BCS: Spanish National Cancer Centre Breast Cancer Study; ESTHER: ESTHER Breast Cancer Study; FBCS: ICR Familial Breast Cancer Study; GENICA: Gene Environment Interaction and Breast Cancer in Germany; GESBC: Genetic Epidemiology Study of Breast Cancer by Age 50; HABCS: Hannover Breast Cancer

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