Breast Cancer Res Treat (2016) 159:433–442
DOI 10.1007/s10549-016-3952-3

PRECLINICAL STUDY

Association study confirms two susceptibility loci for breast cancer in Chinese Han women

Minggui Xu[1,2,3] · Yihui Xu[1,2] · Mengyun Chen[1,2,3] · Yang li[3] · Wei li[1] · Jun Zhu[3] · Mingjun Zhang[1] · Zhendong Chen[1] · Xuejun Zhang[3,4] · Jianjun liu[2] · Bo Zhang[1,2]

Received: 25 May 2016 / Accepted: 18 August 2016 / Published online: 29 August 2016

Abstract To date, many loci associated with breast cancer have been identified through genome-wide association studies; most of these studies were conducted using populations of European descent. Thus, it is not clear whether these susceptibility loci are also risk factors for Chinese populations. We selected and genotyped 32 single nucleotide polymorphisms (SNPs) using the Sequenom iPLEX platform in a female Chinese cohort of 3036 breast cancer cases and 3036 healthy controls. A total of 23 SNPs passed the quality control test. The associations of these SNPs with disease susceptibility were assessed using logistic regression, adjusting for age. The Bonferroni correction was used to conservatively account for multiple testing, and the threshold for statistical significance was $P < 2.17 \times 10^{-3}$ (0.05/23). We confirmed ten risk-associated variants within three reported breast cancer susceptibility loci in a Chinese Han population: 5q11.2 (rs16886181, $P = 5.29 \times 10^{-6}$, OR = 1.19; rs1017226, $P = 5.24 \times 10^{-4}$, OR = 1.22; rs16886034, $P = 2.00 \times 10^{-3}$, OR = 1.21; rs16886113, $P = 1.24 \times 10^{-3}$, OR = 1.20; rs16886364, $P = 9.20 \times 10^{-4}$, OR = 1.21; rs16886397, $P = 1.17 \times 10^{-3}$, OR = 1.20; rs16886448, $P = 1.62 \times 10^{-3}$, OR = 1.20; and rs2229882, $P = 5.14 \times 10^{-4}$, OR = 1.31), 5q14.3 (rs421379, $P = 2.83 \times 10^{-13}$, OR = 1.83), and 10q26.1 (rs35054928, $P = 7.73 \times 10^{-6}$, OR = 1.18). The 10q26.1 locus was found to be a susceptibility locus for breast cancer in Chinese Han women in our previous studies. 5q11.2 and 5q14.3 are confirmed here for the first time as susceptibility loci for breast cancer in Chinese Han women. This study reports three breast cancer susceptibility loci that were previously identified in European populations and are also risk factors for Chinese populations. This study may extend the genetic basis of breast cancer in Chinese Han women and highlight the contribution of multiple variants of modest effect.

Keywords Breast cancer · Single nucleotide polymorphisms (SNPs) · Genetics · Association study · Chinese Han women

Minggui Xu, Yihui Xu, and Mengyun Chen contributed equally.

✉ Xuejun Zhang
ayzxj@mail.hf.ah.cn

✉ Jianjun liu
liuj3@gis.a-star.edu.sg

✉ Bo Zhang
alvinbo@163.com

[1] Department of Oncology, No. 2 Hospital, Anhui Medical University, Hefei, Anhui, China

[2] School of Life Sciences, Anhui Medical University, Hefei, Anhui, China

[3] Institute of Dermatology and Department of Dermatology the First Affiliated Hospital, Anhui Medical University, Hefei, Anhui, China

[4] State Key Laboratory Incubation Base of Dermatology, Ministry of National Science and Technology, Hefei, Anhui, China

Introduction

Breast cancer is the most invasive malignant tumor disease in women worldwide [1]. The morbidity and mortality of breast cancer have grown rapidly in both urban and rural areas of China. Breast cancer has become the leading cause of malignancy in Chinese females [2]. 2012 GLOBOCAN data show that in China, the incidence of breast cancer has reached 22.1/100 thousand, and the mortality rate is 5.4/100 thousand [1]. The pathogenesis of breast cancer is complicated, suggesting that genetic factors play a significant role [3, 4]. Recent genome-wide

association studies (GWAS) have discovered numerous risk-associated variants more than 90 common genetic susceptibility genes/loci for breast cancer, as reported in the National Human Genome Research Institute catalog (NHGRI GWAS Catalog, available at:www.genome.gov/gwastudies). However, fewer than 30 loci have been validated in the Chinese Han population [5–10]. Most GWAS have been conducted among women of European ancestry. However, these novel loci in women of European descent tend to be weakly associated with breast cancer in women of Chinese descent [5] or have not been determined in Chinese Han populations. Because of the genetic architecture difference between two ethnic populations, additional validation studies in Chinese Han population are of great interest [11].

We have previously performed three validation studies in Chinese Han women [5, 12, 13] and, in total, have evaluated 84 SNPs that were discovered before 2013 in 47 genes/loci and confirmed nine reported breast cancer susceptibility loci, including *SIAH2*, *INHBB-GLI2,TGFBR2*, *ADAM29*, *FTO, DUSP4-MIR3148, ESR1, FGFR2,* and *TOX3*. For the novel susceptibility loci/genes in Europeans after 2013, in this study, we evaluated these SNPs in Chinese Han women [14–23].

Table 1 The basic breast cancer characteristics

Characteristics	Sample
Cases	
Sample size	3036
Mean age (years) at onset	52.6 ± 10.6
Mean age (years)	51.9 ± 11.2
Familial history of breast cancer	
Familial (%)	7.87 %
Sporadic (%)	92.13 %
ER status	
No. of ER-positive cases (%)	2030 (66.9 %)
No. of ER-negative cases (%)	1006 (33.1 %)
PR status	
No. of PR-positive cases (%)	1898(62.5 %)
No. of PR-negative cases (%)	1138(37.5 %)
HER-2 status	
HER-2 positive cases (%)	953(31.3 %)
HER-2 negative cases (%)	2083(68.7 %)
Controls	
Sample size	3036
Mean age (years)	47.4 ± 9.8

Materials and methods

Subjects

A total of 3036 patients suffering from breast cancer and 3036 healthy controls (female only) were recruited through collaborations with the No. 1 Hospital and No. 2 Hospital of Anhui Medical University in the province of Anhui. The basic breast cancer characteristics are shown in (Table 1). The diagnosis of each case was confirmed by at least two oncologists. All of the enrolled patients were newly diagnosed. All of the Chinese controls were clinically confirmed to be free of breast cancer, other neoplastic diseases, systemic disorders, and a family history of neoplastic diseases (including first-, second-, and third-degree relatives). Uniform criteria were used to recruit patients and controls. The same questionnaire was used to collect the clinical and demographic information of each participant. After written informed consent was obtained, a peripheral blood sample was collected from each participant. This study was approved by the Institutional Ethical Committee of each hospital and was conducted in accordance with the Declaration of Helsinki.

SNP selection

For this study, we choose 32 candidate SNPs that were discovered from other populations after 2013. Most of these studies were conducted on women of European descent. These 32 SNPs represent 22 independent loci that are present in either genes or intergenic regions (Table 2) [14–23].

Genotyping and quality controls

Genotyping analyses were conducted using the Sequenom Mass Array system at the State Key Laboratory Incubation Base of Dermatology, Ministry of National Science and Technology, Hefei, Anhui, China. Genomic DNA was extracted from whole-blood or buffy-coat samples using FlexiGene® DNA kits (QIAGEN, Hilden, Germany). The DNA quality of all of the samples was analyzed using a Nanodrop Spectrophotometer ND-2000 (Thermo Scientific, Wilmington, USA), and agarose gel electrophoresis was performed to ensure the genomic integrity of the samples. Approximately 15 ng of genomic DNA was used to genotype each sample. Locus-specific PCR and detection primers were designed using MassARRAY Assay Design 3.0 software (Sequenom, San Diego, USA). Following the manufacturer's instructions, the DNA samples were amplified by multiplex PCR reactions, and the PCR products were then used for locus-specific single-base extension reactions. The resulting products were desalted and transferred to a 384-element SpectroCHIP array. Allele detection was performed using matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF MS). The mass

Table 2 The 32 candidate SNPs from other population

CHR	SNP	Position (hg18)	Alleles[a]	MAF		*P*	OR $_{\text{reported previously}}$ (95 % CI)	Gene of interest	References
				CEU[b]	CHB[c]				
1	rs72755295	242034263	NA	NA	NA	1.82×10^{-8}	1.19 (1.03–1.39)	EXO1	kyriaki michailidou [21]
1	rs2290854	204516025	T/G	0.31	0.344	2.7×10^{-8}	1.14(1.09–1.20)	MDM4	Fergus J. Couch [15]
1	rs2774307	114670969	T/C	0.2	0.144	8.0×10^{-6}	1.30(1.16–1.47)	SYT6	Sajjad Rafiq [23]
2	rs4442975	217920769	G/T	0.375	0.133	1.7×10^{-43}	0.85 (0.84–0.87)	LOC101928278	Maya Ghoussaini [18]
3	rs6796502	46866866	NA	NA	NA	1.84×10^{-8}	0.92 (0.87–0.98)	PRSS4-PRSS42	kyriaki michailidou [21]
5	rs13162653	16187528	NA	NA	NA	1.08×10^{-10}	0.92 (0.88–0.95)	LOC401176	kyriaki michailidou [21]
5	rs7707921	81538046	NA	NA	NA	5.00×10^{-11}	0.94 (0.90–0.98)	ATG10	kyriaki michailidou [21]
5	rs2229882	56168712	NA	NA	NA	3.63×10^{-7}	1.45(1.32–1.6)	MAP3K1	Habibul Ahsan [14]
5	rs16886181	56029243	T/C	0.192	0.3	5.72×10^{-4}	1.26(1.18–1.34)	MAP3K1	Habibul Ahsan [14]
5	rs16886448	56170813	C/G	0.075	0.067	5.21×10^{-6}	1.37 (1.25–1.49)	MAP3K1	Habibul Ahsan [14]
5	rs16886397	56134276	A/G	0.068	0.068	8.05×10^{-6}	1.36 (1.25–1.49)	MAP3K1	Habibul Ahsan [14]
5	rs16886364	56122344	A/G	0.075	0.067	1.03×10^{-5}	1.36 (1.25–1.48)	MAP3K1	Habibul Ahsan [14]
5	rs16886113	55995035	T/G	0.058	0.089	1.71×10^{-5}	1.35 (1.23–1.47)	MAP3K1	Habibul Ahsan [14]
5	rs1017226	56153392	T/C	0.075	0.067	2.57×10^{-5}	1.33 (1.22–1.45)	MAP3K1	Habibul Ahsan [14]
5	rs7726354	56256483	C/T	0.05	0.033	4.9×10^{-5}	1.37 (1.24–1.50)	MIER3 - GPBP1	Habibul Ahsan [14]
5	rs16886034	55983856	T/C	0.058	0.078	7×10^{-5}	1.36 (1.23–1.51)	MAP3K1	Habibul Ahsan [14]
5	rs421379	91275313	T/C	0.075	0.022	1.0×10^{-6}	1.61(1.33–1.96)	ARRDC3	Sajjad Rafiq [23]
6	rs140068132	151954834	NA	NA	NA	9.0×10^{-18}	0.60(0.53–0.67)	LOC105378058	Laura Fejerman [16]
7	rs4593472	130667121	C/T	0.267	0.122	1.83×10^{-9}	0.92 (0.88–0.96)	LINC-PINT	kyriaki michailidou [21]
8	rs13365225	36858483	A/G	0.177	0.356	1.06×10^{-8}	0.89 (0.85–0.93)	PRL26P25-SMARCE1P4	kyriaki michailidou [21]
8	rs13267382	117209548	NA	NA	NA	1.72×10^{-8}	1.07 (1.03–1.12)	LINC00536	kyriaki michailidou [21]
9	rs676256	110895353	C/T	0.407	0.129	1.58×10^{-25}	0.90 (0.88–0.92)	LOC105376214	Nick Orr [22]
9	rs10816625	110837073	A/G	0.1	0.467	7.89×10^{-09}	1.12 (1.08–1.17)	LOC105376214	Nick Orr [22]
10	rs35054928	123340432	NA	NA	NA	6.8×10^{-131}	1.27 (1.24–1.29)	FGFR2	Kerstin B. Meyer [20]
10	rs45631563	123349324	NA	NA	NA	3.8×10^{-15}	0.8(0.76–0.85)	FGFR2	Kerstin B. Meyer [20]

Table 2 continued

CHR	SNP	Position (hg18)	Alleles[a]	MAF		*P*	OR $_{\text{reported previously}}$ (95 % CI)	Gene of interest	References
				CEU[b]	CHB[c]				
11	rs1047739	61919693	NA	NA	NA	0.0002	1.06 (1.02–1.10)	INCENP	Maria Kabisch [19]
11	rs554219	69331642	G/C	0.119	0.012	1.0×10^{-66}	1.33(1.28–1.37)	LOC101928292-CCND1	Juliet D. French [17]
11	rs75915166	69379161	NA	NA	NA	2.7×10^{-46}	1.38(1.32–1.44)	LOC101928292-CCND1	Juliet D. French [17]
11	rs537626	69307695	C/G	0.0167	0	3.74×10^{-4}	1.29 (1.21–1.37)	LOC101928292	Habibul Ahsan [14]
17	rs745570	77781725	T/G	0.492	0.356	1.40×10^{-9}	0.94 (0.91–0.98)	CBX8-CBX4	kyriaki michailidou [21]
17	rs3785982	9090224	C/T	0.092	0.2	8.0×10^{-6}	1.40(1.21–1.62)	NTN1	Sajjad Rafiq [23]
18	rs6507583	42399590	A/G	0.058	0.167	3.20×10^{-8}	0.91 (0.85–0.98)	SETBP1	kyriaki michailidou [21]

[a] Minor allele/Major allele

[b] Mean minor allele frequency over all European controls in these articles

[c] Mean minor allele frequency in Chinese Han from Beijing (CHB) obtained from HapMap

spectrograms were analyzed by MassARRAY Typer software (Sequenom). The exclusion criteria for the genotyped SNPs included a call rate of <95 % and deviation from Hardy–Weinberg equilibrium (HWE, $P < 0.05/32$) in the controls. In total, 23 SNPs passed the quality control test and were subjected to statistical analysis.

Statistical analysis

The association between the SNPs and breast cancer susceptibility was assessed using logistic regression, adjusting for age. The strength of the association was estimated by calculating the odds ratio (OR) with a 95 % confidence interval (CI). The Hardy–Weinberg equilibrium was assessed using the Chi-square test. All of the statistics were analyzed using the SPSS 13.0 and Plink 1.07 software packages. In total, 23 SNPs were subjected to statistical analysis. Conservatively accounting for multiple comparisons by Bonferroni correction, the threshold for statistical significance was $P < 2.17 \times 10^{-3}$ (0.05/23).

Results

To identify additional susceptibility loci associated with breast cancer in the Han Chinese population, we selected 32 SNPs from studies of breast cancer susceptibility genes/loci that were published after 2013 for a validation study (Table 2). Of the 32 SNPs, 9 were excluded from further analyses because they did not pass the quality control tests. Of the remaining 23 SNPs (Table 3), 10 SNPs were significantly associated with breast cancer in Chinese women. For 5q11.2, eight reported SNPs were replicated (rs16886181, $P = 5.29 \times 10^{-6}$, OR = 1.19; rs1017226, $P = 5.24 \times 10^{-4}$, OR = 1.22; rs16886034, $P = 2.00 \times 10^{-3}$, OR = 1.21; rs16886113, $P = 1.24 \times 10^{-3}$, OR = 1.20; rs16886364, $P = 9.20 \times 10^{-4}$, OR = 1.21; rs16886397, $P = 1.17 \times 10^{-3}$, OR = 1.20; rs16886448, $P = 1.62 \times 10^{-3}$, OR = 1.20; and rs2229882, $P = 5.14 \times 10^{-4}$, OR = 1.31). For 5q14.3, one reported SNP was replicated (rs421379, $P = 2.83 \times 10^{-13}$, OR = 1.83). For 10q26.1, one reported SNP was replicated (rs35054928, $P = 7.73 \times 10^{-6}$, OR = 1.18). 5q11.2 and 5q14.3 are first confirmed here as susceptibility loci for breast cancer in Chinese Han women. 10q26.1 has been confirmed in our previous studies as a susceptibility locus for breast cancer in Chinese Han women [5].

Discussion

We could not confirm all of the SNPs that we selected, which were confirmed in other populations. Such SNPs were in linkage disequilibrium (LD), with the functional variant potentially being located somewhere in particular chromosomal regions. Because of differences in LD patterns according to genetic ancestry, SNPs identified in studies including individuals of other population may not be in high LD with the functional variant in Chinese Han women [24, 25]. Genetic interactions with other SNPs that differ in frequency between populations could also manifest as effect heterogeneity [11].

Table 3 Association of breast cancer susceptibility in the Chinese population with 23 SNPs previously identified by GWAS

CHR	SNP	Alleles[a]	MAF[b]		*P*	OR (95 % CI)	p-hwe[c]	Call rate
			Case	Control				
1	rs2290854	A/G	0.3225	0.3252	7.55×10^{-1}	0.99 (0.92–1.07)	0.02	0.99
1	rs2774307	A/G	0.1161	0.1197	5.45×10^{-1}	0.97 (0.86–1.08)	0.86	0.99
2	rs4442975	G/T	0.1117	0.1106	8.39×10^{-1}	1.01 (0.90–1.13)	0.85	0.99
3	rs6796502	A/G	0.1469	0.1600	4.62×10^{-2}	0.90 (0.82–1.00)	1.00	0.99
5	rs1017226	C/T	0.1269	0.1066	5.24×10^{-4}	1.22 (1.09–1.36)	0.50	0.99
5	rs16886034	C/T	0.1103	0.0933	2.00×10^{-3}	1.21 (1.07–1.36)	1.00	0.99
5	rs16886113	G/T	0.1311	0.1117	1.24×10^{-3}	1.20 (1.07–1.34)	0.85	0.98
5	rs16886181	C/T	0.3567	0.3174	5.29×10^{-6}	1.19 (1.11–1.29)	0.18	0.99
5	rs16886364	G/A	0.1268	0.1074	9.20×10^{-4}	1.21 (1.08–1.35)	0.63	0.99
5	rs16886397	G/A	0.1250	0.1061	1.17×10^{-3}	1.20 (1.08–1.35)	0.63	0.99
5	rs16886448	G/C	0.1224	0.1042	1.62×10^{-3}	1.20 (1.07–1.34)	0.38	0.99
5	rs2229882	T/C	0.0660	0.0511	5.14×10^{-4}	1.31 (1.13–1.53)	0.85	0.99
5	rs421379	T/C	0.0689	0.0388	2.83×10^{-13}	1.83 (1.55–2.16)	0.13	0.99
5	rs7726354	T/C	0.0655	0.0527	2.91×10^{-3}	1.26 (1.08–1.47)	0.72	0.99
7	rs4593472	T/C	0.1388	0.1570	4.82×10^{-3}	0.87 (0.78–0.96)	0.89	0.99
8	rs13267382	G/A	0.4481	0.4402	3.81×10^{-1}	1.03 (0.96–1.11)	0.55	0.99
8	rs13365225	G/A	0.3374	0.3286	3.05×10^{-1}	1.04 (0.96–1.12)	0.41	0.99
9	rs676256	C/T	0.0399	0.0419	5.86×10^{-1}	0.95 (0.79–1.14)	1.00	0.98
9	rs10816625	G/A	0.4930	0.4868	4.95×10^{-1}	1.03 (0.95–1.10)	0.83	0.99
10	rs35054928	C/DEL	0.4768	0.4361	7.73×10^{-6}	1.18 (1.10–1.27)	0.71	0.99
11	rs1047739	T/C	0.0547	0.0494	1.91×10^{-1}	1.11 (0.95–1.31)	0.44	0.99
17	rs3785982	T/C	0.1874	0.1867	9.13×10^{-1}	1.01 (0.92–1.10)	1.00	0.99
17	rs745570	G/A	0.3738	0.3939	2.36×10^{-2}	0.92 (0.85–0.99)	0.25	0.99

[a] Minor allele/Major allele

[b] Minor allele frequency

[c] HWE mean Hardy–Weinberg equilibrium

In the present study, we confirmed for the first time two breast cancer susceptibility loci in Chinese Han women: 5q11.2 (rs16886181, rs1017226, rs16886034, rs16886113, rs16886364, rs16886397, rs16886448, and rs2229882) and 5q14.3 (rs421379).

At 5q11.2, eight SNPs were confirmed. These SNPs were respectively located in the intronic region of the mitogen-activated protein kinase kinase kinase 1(*MAP3K1*) gene. *MAP3K1* is of particular interest for breast carcinogenesis among the genes located in the 5q11.2 region. The *MAP3K1* gene is involved in the MAPK signaling pathway and plays a pivotal role in regulating the transcription of important cancer genes by encoding MAP3K1, a serine/threonine kinase protein [26]. MAPKs include MAP3K1, MAP2K, and MAPK, which regulate diverse cellular functions by modulating transcription factor activity to affect gene expression. Among these, MAP3K1 regulates immune system development and function, injury repair, vasculature remodeling, and tumor progression [27, 28]. Recently, several studies have demonstrated that *MAP3K1* is a genetic susceptibility marker for some tumors, such as breast cancer and gastric cancer [29–31]. Breast cancer risk alleles, such as rs62355900 [iCHAV1], rs16886397 [iCHAV2a], and rs17432750 [iCHAV3], increase MAP3K1 expression in vivo and might promote breast cancer cell survival [29]. A recent study investigated the impact of MAP3K1-targeting miRNA on the growth and invasive behavior of breast cancer in vitro and in vivo by delivering using a miRNA-expressing lentivirus system an artificial miRNA (Map3k1 amiRNA) that targets MAP3K1 to 4T1 breast cancer cells; this finding suggests that MAP3K1-targeting artificial miRNA may have promising therapeutic effects for the treatment of breast cancer [30]. Another study noted that the MAP3K1 protein expression level in breast cancer cells was higher than that in normal mammary gland cells. MAP3K1 siRNA transfection can significantly reduce the expression level of MAP3K1 and enhance paclitaxel-induced cell proliferation inhibition and cell cycle arrest in breast cancer cells. Targeting MAP3K1 expression through small RNA interference can promote the therapeutic effects of paclitaxel on breast cancer [27].

The SNP rs421379 lies upstream of the arrestin domain containing 3 (*ARRDC3*) gene on chromosome 5q14.3. The associated SNP rs421379 is located in the 5′ region of the

ARRDC3 gene and might affect a transcription binding site and *ARRDC3* gene expression, permitting the development of a more aggressive and invasive tumor [23]. The *ARRDC3* gene belongs to the arrestin gene family and functions in a novel regulatory pathway that controls the cell surface adhesion molecule, b-4 integrin (ITGb4), a protein associated with aggressive tumor behavior [23, 32]. The upregulation of the *ARRDC3* gene in a breast cancer cell line has been shown to repress cell proliferation, migration, invasion, and in vivo tumorigenesis [33]. The data indicate that ARRDC3 binds directly to a phosphorylated form of ITGb4, leading to its internalization, ubiquitination, and ultimate degradation, which identifies the ARRDC3-ITGb4 pathway as a new therapeutic target in breast cancer and demonstrates the importance of connecting genetic arrays with mechanistic studies searching for new treatments [33]. A gene cluster at 5q11-q23 that includes *ARRDC3* was deleted in 17 % of breast cancer tumor tissue [34].

Conclusions

In summary, we performed a large-scale case–control study and for the first time confirmed two reported breast cancer susceptibility loci (5q11.2 and 5q14.3) in a Chinese Han population; these loci have already been confirmed in other populations. We once again confirmed 10q26.1, a susceptibility locus for breast cancer in Chinese Han women. These data, along with data on other reported susceptibility loci, collectively demonstrate the complexity of the heritable contribution to the pathogenesis of breast cancer and highlight the contribution of multiple variants of modest effect. Moreover, further investigation and functional studies will be required if we are to advance our understanding of how the loci confirmed in this study influence the etiology of breast cancer.

Acknowledgments We thank the individuals and families who participated in this project. We would also like to thank the participants who helped to collect samples from the Genetic Resources Collection Collaboration, China. We thank the State Key Laboratory Incubation Base of Dermatology, Ministry of National Science and Technology (Hefei, China). This project was supported by the Young Program of the National Natural Science Foundation of China (81301771).

Compliance with ethical standards

Conflict of interests The authors declare that they have no competing interests.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. CA Cancer J Clin 65(2):87–108. doi:10.3322/caac.21262
2. Yang L, Li LD, Chen YD, Parkin DM (2006) Time trends, estimates and projects for breast cancer incidence and mortality in China. Zhonghua zhong liu za zhi (Chin J Oncol) 28(6): 438–440
3. Balmain A, Gray J, Ponder B (2003) The genetics and genomics of cancer. Nat Genet 33(Suppl):238–244. doi:10.1038/ng1107
4. Nathanson KL, Wooster R, Weber BL (2001) Breast cancer genetics: what we know and what we need. Nat Med 7(5):552–556. doi:10.1038/87876
5. Barzan D, Veldwijk MR, Herskind C, Li Y, Zhang B, Sperk E, Du WD, Zhang XJ, Wenz F (2013) Comparison of genetic variation of breast cancer susceptibility genes in Chinese and German populations. Eur J Hum Genet EJHG 21(11):1286–1292. doi:10.1038/ejhg.2013.38
6. He Y, Liu H, Chen Q, Sun X, Liu C, Shao Y (2016) Relationship between five GWAS-identified single nucleotide polymorphisms and female breast cancer in the Chinese Han population. Tumour Biol. doi:10.1007/s13277-016-4795-6
7. Jiang Y, Han J, Liu J, Zhang G, Wang L, Liu F, Zhang X, Zhao Y, Pang D (2011) Risk of genome-wide association study newly identified genetic variants for breast cancer in Chinese women of Heilongjiang Province. Breast Cancer Res Treat 128(1):251–257. doi:10.1007/s10549-010-1327-8
8. Liang H, Li H, Yang X, Chen L, Zhu A, Sun M, Ye C, Li M (2016) Associations of genetic variants at nongenic susceptibility loci with breast cancer risk and heterogeneity by tumor subtype in Southern Han Chinese women. BioMed Res Int 2016:3065493. doi:10.1155/2016/3065493
9. Liang H, Yang X, Chen L, Li H, Zhu A, Sun M, Wang H, Li M (2015) Heterogeneity of breast cancer associations with common genetic variants in FGFR2 according to the intrinsic subtypes in Southern Han Chinese women. BioMed Res Int 2015:626948. doi:10.1155/2015/626948
10. Song A, Zhao L, Li Y, Wu L, Li Y, Liu X, Lan S (2016) Haplotypes of the MTHFR gene are associated with an increased risk of breast cancer in a Han Chinese population in Gansu province. IUBMB Life 68(7):526–534. doi:10.1002/iub.1509
11. Long J, Shu XO, Cai Q, Gao YT, Zheng Y, Li G, Li C, Gu K, Wen W, Xiang YB, Lu W, Zheng W (2010) Evaluation of breast cancer susceptibility loci in Chinese women. Cancer Epidemiol Biomark Prev 19(9):2357–2365. doi:10.1158/1055-9965.epi-10-0054
12. Zhang B, Li Y, Li L, Chen M, Zhang C, Zuo XB, Zhou FS, Liang B, Zhu J, Li P, Huang ZL, Xuan H, Li W, Chen ZD (2014) Association study of susceptibility loci with specific breast cancer subtypes in Chinese women. Breast Cancer Res Treat 146(3):503–514. doi:10.1007/s10549-014-3041-4
13. Zhang B, Li Y, Zheng X, Zuo X, Zhou F, Liang B, Zhu J, Li P, Ding Y, Huang Z, Wang B, Chen Z (2013) A common variant in the SIAH2 locus is associated with estrogen receptor-positive breast cancer in the Chinese Han population. PLoS One 8(11):e79365. doi:10.1371/journal.pone.0079365
14. Ahsan H, Halpern J, Kibriya MG, Pierce BL, Tong L, Gamazon E, McGuire V, Felberg A, Shi J, Jasmine F, Roy S, Brutus R, Argos M, Melkonian S, Chang-Claude J, Andrulis I, Hopper JL, John EM, Malone K, Ursin G, Gammon MD, Thomas DC, Seminara D, Casey G, Knight JA, Southey MC, Giles GG, Santella RM, Lee E, Conti D, Duggan D, Gallinger S, Haile R, Jenkins M, Lindor NM, Newcomb P, Michailidou K, Apicella C, Park DJ, Peto J, Fletcher O, dos Santos Silva I, Lathrop M, Hunter DJ, Chanock SJ, Meindl A, Schmutzler RK, Muller-Myhsok B, Lochmann M, Beckmann L, Hein R, Makalic E, Schmidt DF, Bui QM, Stone J, Flesch-Janys D, Dahmen N, Nevanlinna H, Aittomaki K, Blomqvist C, Hall P, Czene K, Irwanto A, Liu J, Rahman N, Turnbull C, Dunning AM, Pharoah P, Waisfisz Q, Meijers-Heijboer H, Uitterlinden AG, Rivadeneira

F, Nicolae D, Easton DF, Cox NJ, Whittemore AS (2014) A genome-wide association study of early-onset breast cancer identifies PFKM as a novel breast cancer gene and supports a common genetic spectrum for breast cancer at any age. Cancer Epidemiol Biomark Prev 23(4):658–669. doi:10.1158/1055-9965.epi-13-0340

15. Couch FJ, Wang X, McGuffog L, Lee A, Olswold C, Kuchenbaecker KB, Soucy P, Fredericksen Z, Barrowdale D, Dennis J, Gaudet MM, Dicks E, Kosel M, Healey S, Sinilnikova OM, Bacot F, Vincent D, Hogervorst FB, Peock S, Stoppa-Lyonnet D, Jakubowska A, Radice P, Schmutzler RK, Domchek SM, Piedmonte M, Singer CF, Friedman E, Thomassen M, Hansen TV, Neuhausen SL, Szabo CI, Blanco I, Greene MH, Karlan BY, Garber J, Phelan CM, Weitzel JN, Montagna M, Olah E, Andrulis IL, Godwin AK, Yannoukakos D, Goldgar DE, Caldes T, Nevanlinna H, Osorio A, Terry MB, Daly MB, van Rensburg EJ, Hamann U, Ramus SJ, Toland AE, Caligo MA, Olopade OI, Tung N, Claes K, Beattie MS, Southey MC, Imyanitov EN, Tischkowitz M, Janavicius R, John EM, Kwong A, Diez O, Balmana J, Barkardottir RB, Arun BK, Rennert G, Teo SH, Ganz PA, Campbell I, van der Hout AH, van Deurzen CH, Seynaeve C, Gomez Garcia EB, van Leeuwen FE, Meijers-Heijboer HE, Gille JJ, Ausems MG, Blok MJ, Ligtenberg MJ, Rookus MA, Devilee P, Verhoef S, van Os TA, Wijnen JT, Frost D, Ellis S, Fineberg E, Platte R, Evans DG, Izatt L, Eeles RA, Adlard J, Eccles DM, Cook J, Brewer C, Douglas F, Hodgson S, Morrison PJ, Side LE, Donaldson A, Houghton C, Rogers MT, Dorkins H, Eason J, Gregory H, McCann E, Murray A, Calender A, Hardouin A, Berthet P, Delnatte C, Nogues C, Lasset C, Houdayer C, Leroux D, Rouleau E, Prieur F, Damiola F, Sobol H, Coupier I, Venat-Bouvet L, Castera L, Gauthier-Villars M, Leone M, Pujol P, Mazoyer S, Bignon YJ, Zlowocka-Perlowska E, Gronwald J, Lubinski J, Durda K, Jaworska K, Huzarski T, Spurdle AB, Viel A, Peissel B, Bonanni B, Melloni G, Ottini L, Papi L, Varesco L, Tibiletti MG, Peterlongo P, Volorio S, Manoukian S, Pensotti V, Arnold N, Engel C, Deissler H, Gadzicki D, Gehrig A, Kast K, Rhiem K, Meindl A, Niederacher D, Ditsch N, Plendl H, Preisler-Adams S, Engert S, Sutter C, Varon-Mateeva R, Wappenschmidt B, Weber BH, Arver B, Stenmark-Askmalm M, Loman N, Rosenquist R, Einbeigi Z, Nathanson KL, Rebbeck TR, Blank SV, Cohn DE, Rodriguez GC, Small L, Friedlander M, Bae-Jump VL, Fink-Retter A, Rappaport C, Gschwantler-Kaulich D, Pfeiler G, Tea MK, Lindor NM, Kaufman B, Shimon Paluch S, Laitman Y, Skytte AB, Gerdes AM, Pedersen IS, Moeller ST, Kruse TA, Jensen UB, Vijai J, Sarrel K, Robson M, Kauff N, Mulligan AM, Glendon G, Ozcelik H, Ejlertsen B, Nielsen FC, Jonson L, Andersen MK, Ding YC, Steele L, Foretova L, Teule A, Lazaro C, Brunet J, Pujana MA, Mai PL, Loud JT, Walsh C, Lester J, Orsulic S, Narod SA, Herzog J, Sand SR, Tognazzo S, Agata S, Vaszko T, Weaver J, Stavropoulou AV, Buys SS, Romero A, de la Hoya M, Aittomaki K, Muranen TA, Duran M, Chung WK, Lasa A, Dorfling CM, Miron A, Benitez J, Senter L, Huo D, Chan SB, Sokolenko AP, Chiquette J, Tihomirova L, Friebel TM, Agnarsson BA, Lu KH, Lejbkowicz F, James PA, Hall P, Dunning AM, Tessier D, Cunningham J, Slager SL, Wang C, Hart S, Stevens K, Simard J, Pastinen T, Pankratz VS, Offit K, Easton DF, Chenevix-Trench G, Antoniou AC (2013) Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet 9(3):e1003212. doi:10.1371/journal.pgen.1003212
16. Fejerman L, Ahmadiyeh N, Hu D, Huntsman S, Beckman KB, Caswell JL, Tsung K, John EM, Torres-Mejia G, Carvajal-Carmona L, Echeverry MM, Tuazon AM, Ramirez C, Gignoux CR, Eng C, Gonzalez-Burchard E, Henderson B, Le Marchand L, Kooperberg C, Hou L, Agalliu I, Kraft P, Lindstrom S, Perez-Stable EJ, Haiman CA, Ziv E (2014) Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25. Nat Commun 5:5260. doi:10.1038/ncomms6260
17. French JD, Ghoussaini M, Edwards SL, Meyer KB, Michailidou K, Ahmed S, Khan S, Maranian MJ, O'Reilly M, Hillman KM, Betts JA, Carroll T, Bailey PJ, Dicks E, Beesley J, Tyrer J, Maia AT, Beck A, Knoblauch NW, Chen C, Kraft P, Barnes D, Gonzalez-Neira A, Alonso MR, Herrero D, Tessier DC, Vincent D, Bacot F, Luccarini C, Baynes C, Conroy D, Dennis J, Bolla MK, Wang Q, Hopper JL, Southey MC, Schmidt MK, Broeks A, Verhoef S, Cornelissen S, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Fasching PA, Loehberg CR, Ekici AB, Beckmann MW, Peto J, dos Santos Silva I, Johnson N, Aitken Z, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Guenel P, Truong T, Laurent-Puig P, Menegaux F, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Milne RL, Zamora MP, Arias Perez JI, Benitez J, Anton-Culver H, Brenner H, Muller H, Arndt V, Stegmaier C, Meindl A, Lichtner P, Schmutzler RK, Engel C, Brauch H, Hamann U, Justenhoven C, Aaltonen K, Heikkila P, Aittomaki K, Blomqvist C, Matsuo K, Ito H, Iwata H, Sueta A, Bogdanova NV, Antonenkova NN, Dork T, Lindblom A, Margolin S, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Lambrechts D, Peeters S, Smeets A, Floris G, Chang-Claude J, Rudolph A, Nickels S, Flesch-Janys D, Radice P, Peterlongo P, Bonanni B, Sardella D, Couch FJ, Wang X, Pankratz VS, Lee A, Giles GG, Severi G, Baglietto L, Haiman CA, Henderson BE, Schumacher F, Le Marchand L, Simard J, Goldberg MS, Labreche F, Dumont M, Teo SH, Yip CH, Ng CH, Vithana EN, Kristensen V, Zheng W, Deming-Halverson S, Shrubsole M, Long J, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Andrulis IL, Knight JA, Glendon G, Mulligan AM, Devilee P, Seynaeve C, Garcia-Closas M, Figueroa J, Chanock SJ, Lissowska J, Czene K, Klevebring D, Schoof N, Hooning MJ, Martens JW, Collee JM, Tilanus-Linthorst M, Hall P, Li J, Liu J, Humphreys K, Shu XO, Lu W, Gao YT, Cai H, Cox A, Balasubramanian SP, Blot W, Signorello LB, Cai Q, Pharoah PD, Healey CS, Shah M, Pooley KA, Kang D, Yoo KY, Noh DY, Hartman M, Miao H, Sng JH, Sim X, Jakubowska A, Lubinski J, Jaworska-Bieniek K, Durda K, Sangrajrang S, Gaborieau V, McKay J, Toland AE, Ambrosone CB, Yannoukakos D, Godwin AK, Shen CY, Hsiung CN, Wu PE, Chen ST, Swerdlow A, Ashworth A, Orr N, Schoemaker MJ, Ponder BA, Nevanlinna H, Brown MA, Chenevix-Trench G, Easton DF, Dunning AM (2013) Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. Am J Hum Genet 92(4):489–503. doi:10.1016/j.ajhg.2013.01.002
18. Ghoussaini M, Edwards SL, Michailidou K, Nord S, Cowper-Sal Lari R, Desai K, Kar S, Hillman KM, Kaufmann S, Glubb DM, Beesley J, Dennis J, Bolla MK, Wang Q, Dicks E, Guo Q, Schmidt MK, Shah M, Luben R, Brown J, Czene K, Darabi H, Eriksson M, Klevebring D, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Lambrechts D, Thienpont B, Neven P, Wildiers H, Broeks A, Van't Veer LJ, Th Rutgers EJ, Couch FJ, Olson JE, Hallberg E, Vachon C, Chang-Claude J, Rudolph A, Seibold P, Flesch-Janys D, Peto J, Dos-Santos-Silva I, Gibson L, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Hall P, Li J, Liu J, Humphreys K, Kang D, Choi' JY, Park SK, Noh DY, Matsuo K, Ito H, Iwata H, Yatabe Y, Guenel P, Truong T, Menegaux F, Sanchez M, Burwinkel B, Marme F, Schneeweiss A, Sohn C, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Benitez J, Zamora MP, Perez JI, Menendez P, Shu XO, Lu W, Gao YT, Cai Q, Cox A, Cross SS, Reed MW, Andrulis IL, Knight JA, Glendon G, Tchatchou S, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Haiman CA, Henderson BE, Schumacher F, Le

Marchand L, Lindblom A, Margolin S, Teo SH, Yip CH, Lee DS, Wong TY, Hooning MJ, Martens JW, Collee JM, van Deurzen CH, Hopper JL, Southey MC, Tsimiklis H, Kapuscinski MK, Shen CY, Wu PE, Yu JC, Chen ST, Alnaes GG, Borresen-Dale AL, Giles GG, Milne RL, McLean C, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Hartman M, Miao H, Buhari SA, Teo YY, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Brenner H, Dieffenbach AK, Arndt V, Stegmaier C, Swerdlow A, Ashworth A, Orr N, Schoemaker MJ, Garcia-Closas M, Figueroa J, Chanock SJ, Lissowska J, Simard J, Goldberg MS, Labreche F, Dumont M, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Brauch H, Bruning T, Koto YD, Radice P, Peterlongo P, Bonanni B, Volorio S, Dork T, Bogdanova NV, Helbig S, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Devilee P, Tollenaar RA, Seynaeve C, Van Asperen CJ, Jakubowska A, Lubinski J, Jaworska-Bieniek K, Durda K, Slager S, Toland AE, Ambrosone CB, Yannoukakos D, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Hamann U, Torres D, Zheng W, Long J, Anton-Culver H, Neuhausen SL, Luccarini C, Baynes C, Ahmed S, Maranian M, Healey CS, Gonzalez-Neira A, Pita G, Alonso MR, Alvarez N, Herrero D, Tessier DC, Vincent D, Bacot F, de Santiago I, Carroll J, Caldas C, Brown MA, Lupien M, Kristensen VN, Pharoah PD, Chenevix-Trench G, French JD, Easton DF, Dunning AM (2014) Evidence that breast cancer risk at the 2q35 locus is mediated through IGFBP5 regulation. Nat Commun 4:4999. doi:10.1038/ncomms5999

19. Kabisch M, Lorenzo Bermejo J, Dunnebier T, Ying S, Michailidou K, Bolla MK, Wang Q, Dennis J, Shah M, Perkins BJ, Czene K, Darabi H, Eriksson M, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Lambrechts D, Neven P, Peeters S, Weltens C, Couch FJ, Olson JE, Wang X, Purrington K, Chang-Claude J, Rudolph A, Seibold P, Flesch-Janys D, Peto J, dos-Santos-Silva I, Johnson N, Fletcher O, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Schmidt MK, Broeks A, Cornelissen S, Hogervorst FB, Li J, Brand JS, Humphreys K, Guenel P, Truong T, Menegaux F, Sanchez M, Burwinkel B, Marme F, Yang R, Bugert P, Gonzalez-Neira A, Benitez J, Pilar Zamora M, Arias Perez JI, Cox A, Cross SS, Reed MW, Andrulis IL, Knight JA, Glendon G, Tchatchou S, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Haiman CA, Schumacher F, Henderson BE, Le Marchand L, Lindblom A, Margolin S, Hooning MJ, Hollestelle A, Kriege M, Koppert LB, Hopper JL, Southey MC, Tsimiklis H, Apicella C, Slettedahl S, Toland AE, Vachon C, Yannoukakos D, Giles GG, Milne RL, McLean C, Fasching PA, Ruebner M, Ekici AB, Beckmann MW, Brenner H, Dieffenbach AK, Arndt V, Stegmaier C, Ashworth A, Orr N, Schoemaker MJ, Swerdlow A, Garcia-Closas M, Figueroa J, Chanock SJ, Lissowska J, Goldberg MS, Labreche F, Dumont M, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Brauch H, Bruning T, Ko YD, Radice P, Peterlongo P, Scuvera G, Fortuzzi S, Bogdanova N, Dork T, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Devilee P, Tollenaar RA, Seynaeve C, Van Asperen CJ, Jakubowska A, Lubinski J, Jaworska-Bieniek K, Durda K, Zheng W, Shrubsole MJ, Cai Q, Torres D, Anton-Culver H, Kristensen V, Bacot F, Tessier DC, Vincent D, Luccarini C, Baynes C, Ahmed S, Maranian M, Simard J, Chenevix-Trench G, Hall P, Pharoah PD, Dunning AM, Easton DF, Hamann U (2015) Inherited variants in the inner centromere protein (INCENP) gene of the chromosomal passenger complex contribute to the susceptibility of ER-negative breast cancer. Carcinogenesis 36(2):256–271. doi:10.1093/carcin/bgu326

20. Meyer KB, O'Reilly M, Michailidou K, Carlebur S, Edwards SL, French JD, Prathalingham R, Dennis J, Bolla MK, Wang Q, de Santiago I, Hopper JL, Tsimiklis H, Apicella C, Southey MC, Schmidt MK, Broeks A, Van't Veer LJ, Hogervorst FB, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Fasching PA, Lux MP, Ekici AB, Beckmann MW, Peto J, Dos Santos Silva I, Fletcher O, Johnson N, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Guenel P, Truong T, Laurent-Puig P, Menegaux F, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Milne RL, Zamora MP, Arias JI, Benitez J, Neuhausen S, Anton-Culver H, Ziogas A, Dur CC, Brenner H, Muller H, Arndt V, Stegmaier C, Meindl A, Schmutzler RK, Engel C, Ditsch N, Brauch H, Bruning T, Ko YD, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Matsuo K, Ito H, Iwata H, Yatabe Y, Dork T, Helbig S, Bogdanova NV, Lindblom A, Margolin S, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Chenevix-Trench G, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Lambrechts D, Thienpont B, Christiaens MR, Smeets A, Chang-Claude J, Rudolph A, Seibold P, Flesch-Janys D, Radice P, Peterlongo P, Bonanni B, Bernard L, Couch FJ, Olson JE, Wang X, Purrington K, Giles GG, Severi G, Baglietto L, McLean C, Haiman CA, Henderson BE, Schumacher F, Le Marchand L, Simard J, Goldberg MS, Labreche F, Dumont M, Teo SH, Yip CH, Phuah SY, Kristensen V, Grenaker Alnaes G, Borresen-Dale AL, Zheng W, Deming-Halverson S, Shrubsole M, Long J, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Kauppila S, Andrulis IL, Knight JA, Glendon G, Tchatchou S, Devilee P, Tollenaar RA, Seynaeve CM, Garcia-Closas M, Figueroa J, Chanock SJ, Lissowska J, Czene K, Darabi H, Eriksson K, Hooning MJ, Martens JW, van den Ouweland AM, van Deurzen CH, Hall P, Li J, Liu J, Humphreys K, Shu XO, Lu W, Gao YT, Cai H, Cox A, Reed MW, Blot W, Signorello LB, Cai Q, Pharoah PD, Ghoussaini M, Harrington P, Tyrer J, Kang D, Choi JY, Park SK, Noh DY, Hartman M, Hui M, Lim WY, Buhari SA, Hamann U, Forsti A, Rudiger T, Ulmer HU, Jakubowska A, Lubinski J, Jaworska K, Durda K, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Vachon C, Slager S, Fostira F, Pilarski R, Shen CY, Hsiung CN, Wu PE, Hou MF, Swerdlow A, Ashworth A, Orr N, Schoemaker MJ, Ponder BA, Dunning AM, Easton DF (2013) Fine-scale mapping of the FGFR2 breast cancer risk locus: putative functional variants differentially bind FOXA1 and E2F1. Am J Hum Genet 93(6):1046–1060. doi:10.1016/j.ajhg.2013.10.026

21. Michailidou K, Beesley J, Lindstrom S, Canisius S, Dennis J, Lush MJ, Maranian MJ, Bolla MK, Wang Q, Shah M, Perkins BJ, Czene K, Eriksson M, Darabi H, Brand JS, Bojesen SE, Nordestgaard BG, Flyger H, Nielsen SF, Rahman N, Turnbull C, Fletcher O, Peto J, Gibson L, dos-Santos-Silva I, Chang-Claude J, Flesch-Janys D, Rudolph A, Eilber U, Behrens S, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Khan S, Aaltonen K, Ahsan H, Kibriya MG, Whittemore AS, John EM, Malone KE, Gammon MD, Santella RM, Ursin G, Makalic E, Schmidt DF, Casey G, Hunter DJ, Gapstur SM, Gaudet MM, Diver WR, Haiman CA, Schumacher F, Henderson BE, Le Marchand L, Berg CD, Chanock SJ, Figueroa J, Hoover RN, Lambrechts D, Neven P, Wildiers H, van Limbergen E, Schmidt MK, Broeks A, Verhoef S, Cornelissen S, Couch FJ, Olson JE, Hallberg E, Vachon C, Waisfisz Q, Meijers-Heijboer H, Adank MA, van der Luijt RB, Li J, Liu J, Humphreys K, Kang D, Choi JY, Park SK, Yoo KY, Matsuo K, Ito H, Iwata H, Tajima K, Guenel P, Truong T, Mulot C, Sanchez M, Burwinkel B, Marme F, Surowy H, Sohn C, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Gonzalez-Neira A, Benitez J, Zamora MP, Perez JI, Shu XO, Lu W, Gao YT, Cai H, Cox A, Cross SS, Reed MW, Andrulis IL, Knight JA, Glendon G, Mulligan AM, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Lindblom A, Margolin S, Teo SH, Yip CH, Taib NA, Tan GH, Hooning MJ, Hollestelle A, Martens JW, Collee JM, Blot W, Signorello LB, Cai Q, Hopper JL, Southey MC, Tsimiklis H, Apicella C, Shen CY, Hsiung CN, Wu PE, Hou MF, Kristensen VN, Nord S, Alnaes GI, Giles GG, Milne RL, McLean C, Canzian F, Trichopoulos D, Peeters P, Lund E, Sund M, Khaw KT, Gunter MJ, Palli D, Mortensen LM, Dossus L, Huerta JM,

Meindl A, Schmutzler RK, Sutter C, Yang R, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Hartman M, Miao H, Chia KS, Chan CW, Fasching PA, Hein A, Beckmann MW, Haeberle L, Brenner H, Dieffenbach AK, Arndt V, Stegmaier C, Ashworth A, Orr N, Schoemaker MJ, Swerdlow AJ, Brinton L, Garcia-Closas M, Zheng W, Halverson SL, Shrubsole M, Long J, Goldberg MS, Labreche F, Dumont M, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Bruning T, Radice P, Peterlongo P, Manoukian S, Bernard L, Bogdanova NV, Dork T, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Devilee P, Tollenaar RA, Seynaeve C, Van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Huzarski T, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Slager S, Toland AE, Ambrosone CB, Yannoukakos D, Kabisch M, Torres D, Neuhausen SL, Anton-Culver H, Luccarini C, Baynes C, Ahmed S, Healey CS, Tessier DC, Vincent D, Bacot F, Pita G, Alonso MR, Alvarez N, Herrero D, Simard J, Pharoah PP, Kraft P, Dunning AM, Chenevix-Trench G, Hall P, Easton DF (2015) Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet 47(4):373–380. doi:10.1038/ng.3242

22. Orr N, Dudbridge F, Dryden N, Maguire S, Novo D, Perrakis E, Johnson N, Ghoussaini M, Hopper JL, Southey MC, Apicella C, Stone J, Schmidt MK, Broeks A, Van't Veer LJ, Hogervorst FB, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Gibson L, Aitken Z, Warren H, Sawyer E, Tomlinson I, Kerin MJ, Miller N, Burwinkel B, Marme F, Schneeweiss A, Sohn C, Guenel P, Truong T, Cordina-Duverger E, Sanchez M, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Benitez J, Zamora MP, Arias Perez JI, Menendez P, Anton-Culver H, Neuhausen SL, Brenner H, Dieffenbach AK, Arndt V, Stegmaier C, Hamann U, Brauch H, Justenhoven C, Bruning T, Ko YD, Nevanlinna H, Aittomaki K, Blomqvist C, Khan S, Bogdanova N, Dork T, Lindblom A, Margolin S, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Chenevix-Trench G, Beesley J, Lambrechts D, Moisse M, Floris G, Beuselinck B, Chang-Claude J, Rudolph A, Seibold P, Flesch-Janys D, Radice P, Peterlongo P, Peissel B, Pensotti V, Couch FJ, Olson JE, Slettedahl S, Vachon C, Giles GG, Milne RL, McLean C, Haiman CA, Henderson BE, Schumacher F, Le Marchand L, Simard J, Goldberg MS, Labreche F, Dumont M, Kristensen V, Alnaes GG, Nord S, Borresen-Dale AL, Zheng W, Deming-Halverson S, Shrubsole M, Long J, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Andrulis IL, Knight JA, Glendon G, Tchatchou S, Devilee P, Tollenaar RA, Seynaeve CM, Van Asperen CJ, Garcia-Closas M, Figueroa J, Chanock SJ, Lissowska J, Czene K, Darabi H, Eriksson M, Klevebring D, Hooning MJ, Hollestelle A, van Deurzen CH, Kriege M, Hall P, Li J, Liu J, Humphreys K, Cox A, Cross SS, Reed MW, Pharoah PD, Dunning AM, Shah M, Perkins BJ, Jakubowska A, Lubinski J, Jaworska-Bieniek K, Durda K, Ashworth A, Swerdlow A, Jones M, Schoemaker MJ, Meindl A, Schmutzler RK, Olswold C, Slager S, Toland AE, Yannoukakos D, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Matsuo K, Ito H, Iwata H, Ishiguro J, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Teo SH, Yip CH, Kang P, Ikram MK, Shu XO, Lu W, Gao YT, Cai H, Kang D, Choi JY, Park SK, Noh DY, Hartman M, Miao H, Lim WY, Lee SC, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Wu PE, Hou MF, Yu JC, Shen CY, Blot W, Cai Q, Signorello LB, Luccarini C, Bayes C, Ahmed S, Maranian M, Healey CS, Gonzalez-Neira A, Pita G, Alonso MR, Alvarez N, Herrero D, Tessier DC, Vincent D, Bacot F, Hunter DJ, Lindstrom S, Dennis J, Michailidou K, Bolla MK, Easton DF, dos Santos Silva I, Fletcher O, Peto J (2015) Fine-mapping identifies two additional breast cancer susceptibility loci at 9q31.2. Hum Mol Genet 24(10):2966–2984. doi:10.1093/hmg/ddv035

23. Rafiq S, Tapper W, Collins A, Khan S, Politopoulos I, Gerty S, Blomqvist C, Couch FJ, Nevanlinna H, Liu J, Eccles D (2013) Identification of inherited genetic variations influencing prognosis in early-onset breast cancer. Cancer Res 73(6):1883–1891. doi:10.1158/0008-5472.can-12-3377

24. Cai Q, Long J, Lu W, Qu S, Wen W, Kang D, Lee JY, Chen K, Shen H, Shen CY, Sung H, Matsuo K, Haiman CA, Khoo US, Ren Z, Iwasaki M, Gu K, Xiang YB, Choi JY, Park SK, Zhang L, Hu Z, Wu PE, Noh DY, Tajima K, Henderson BE, Chan KY, Su F, Kasuga Y, Wang W, Cheng JR, Yoo KY, Lee JY, Zheng H, Liu Y, Shieh YL, Kim SW, Lee JW, Iwata H, Le Marchand L, Chan SY, Xie X, Tsugane S, Lee MH, Wang S, Li G, Levy S, Huang B, Shi J, Delahanty R, Zheng Y, Li C, Gao YT, Shu XO, Zheng W (2011) Genome-wide association study identifies breast cancer risk variant at 10q21.2: results from the Asia Breast Cancer Consortium. Hum Mol Genet 20(24):4991–4999. doi:10.1093/hmg/ddr405

25. Hutter CM, Young AM, Ochs-Balcom HM, Carty CL, Wang T, Chen CT, Rohan TE, Kooperberg C, Peters U (2011) Replication of breast cancer GWAS susceptibility loci in the Women's Health Initiative African American SHARe Study. Cancer Epidemiol Biomark Prev 20(9):1950–1959. doi:10.1158/1055-9965.epi-11-0524

26. Witowsky JA, Johnson GL (2003) Ubiquitylation of MEKK1 inhibits its phosphorylation of MKK1 and MKK4 and activation of the ERK1/2 and JNK pathways. J Biol Chem 278(3):1403–1406. doi:10.1074/jbc.C200616200

27. Hu P, Huang Q, Li Z, Wu X, Ouyang Q, Chen J, Cao Y (2014) Silencing MAP3K1 expression through RNA interference enhances paclitaxel-induced cell cycle arrest in human breast cancer cells. Mol Biol Rep 41(1):19–24. doi:10.1007/s11033-013-2811-0

28. Geh E, Meng Q, Mongan M, Wang J, Takatori A, Zheng Y, Puga A, Lang RA, Xia Y (2011) Mitogen-activated protein kinase kinase kinase 1 (MAP3K1) integrates developmental signals for eyelid closure. Proc Natl Acad Sci USA 108(42):17349–17354. doi:10.1073/pnas.1102297108

29. Glubb DM, Maranian MJ, Michailidou K, Pooley KA, Meyer KB, Kar S, Carlebur S, O'Reilly M, Betts JA, Hillman KM, Kaufmann S, Beesley J, Canisius S, Hopper JL, Southey MC, Tsimiklis H, Apicella C, Schmidt MK, Broeks A, Hogervorst FB, van der Schoot CE, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Fasching PA, Ruebner M, Ekici AB, Beckmann MW, Peto J, dos-Santos-Silva I, Fletcher O, Johnson N, Pharoah PD, Bolla MK, Wang Q, Dennis J, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Burwinkel B, Marme F, Yang R, Surowy H, Guenel P, Truong T, Menegaux F, Sanchez M, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Gonzalez-Neira A, Benitez J, Zamora MP, Arias Perez JI, Anton-Culver H, Neuhausen SL, Brenner H, Dieffenbach AK, Arndt V, Stegmaier C, Meindl A, Schmutzler RK, Brauch H, Ko YD, Bruning T, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Matsuo K, Ito H, Iwata H, Tanaka H, Dork T, Bogdanova NV, Helbig S, Lindblom A, Margolin S, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Lambrechts D, Zhao H, Weltens C, van Limbergen E, Chang-Claude J, Flesch-Janys D, Rudolph A, Seibold P, Radice P, Peterlongo P, Barile M, Capra F, Couch FJ, Olson JE, Hallberg E, Vachon C, Giles GG, Milne RL, McLean C, Haiman CA, Henderson BE, Schumacher F, Le Marchand L, Simard J, Goldberg MS, Labreche F, Dumont M, Teo SH, Yip CH, See MH, Cornes B, Cheng CY, Ikram MK, Kristensen V, Zheng W, Halverson SL, Shrubsole M, Long J, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Kauppila S, Andrulis IL, Knight JA, Glendon G, Tchatchou S, Devilee P, Tollenaar RA, Seynaeve C, Van Asperen CJ, Garcia-Closas M, Figueroa J, Chanock SJ, Lissowska J, Czene K,

Klevebring D, Darabi H, Eriksson M, Hooning MJ, Hollestelle A, Martens JW, Collee JM, Hall P, Li J, Humphreys K, Shu XO, Lu W, Gao YT, Cai H, Cox A, Cross SS, Reed MW, Blot W, Signorello LB, Cai Q, Shah M, Ghoussaini M, Kang D, Choi JY, Park SK, Noh DY, Hartman M, Miao H, Lim WY, Tang A, Hamann U, Torres D, Jakubowska A, Lubinski J, Jaworska K, Durda K, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Olswold C, Slager S, Toland AE, Yannoukakos D, Shen CY, Wu PE, Yu JC, Hou MF, Swerdlow A, Ashworth A, Orr N, Jones M, Pita G, Alonso MR, Alvarez N, Herrero D, Tessier DC, Vincent D, Bacot F, Luccarini C, Baynes C, Ahmed S, Healey CS, Brown MA, Ponder BA, Chenevix-Trench G, Thompson DJ, Edwards SL, Easton DF, Dunning AM, French JD (2015) Fine-scale mapping of the 5q11.2 breast cancer locus reveals at least three independent risk variants regulating MAP3K1. Am J Hum Genet 96(1):5–20. doi:10.1016/j.ajhg.2014.11.009

30. Liu C, Wang S, Zhu S, Wang H, Gu J, Gui Z, Jing J, Hou X, Shao Y (2016) MAP3K1-targeting therapeutic artificial miRNA suppresses the growth and invasion of breast cancer in vivo and in vitro. SpringerPlus 5:11. doi:10.1186/s40064-015-1597-z
31. Pham TT, Angus SP, Johnson GL (2013) MAP3K1: genomic alterations in cancer and function in promoting cell survival or apoptosis. Genes Cancer 4(11–12):419–426. doi:10.1177/1947601913513950
32. Cai Q, Zhang B, Sung H, Low SK, Kweon SS, Lu W, Shi J, Long J, Wen W, Choi JY, Noh DY, Shen CY, Matsuo K, Teo SH, Kim MK, Khoo US, Iwasaki M, Hartman M, Takahashi A, Ashikawa K, Matsuda K, Shin MH, Park MH, Zheng Y, Xiang YB, Ji BT, Park SK, Wu PE, Hsiung CN, Ito H, Kasuga Y, Kang P, Mariapun S, Ahn SH, Kang HS, Chan KY, Man EP, Iwata H, Tsugane S, Miao H, Liao J, Nakamura Y, Kubo M, Delahanty RJ, Zhang Y, Li B, Li C, Gao YT, Shu XO, Kang D, Zheng W (2014) Genome-wide association analysis in East Asians identifies breast cancer susceptibility loci at 1q32.1, 5q14.3 and 15q26.1. Nat Genet 46(8):886–890. doi:10.1038/ng.3041
33. Draheim KM, Chen HB, Tao Q, Moore N, Roche M, Lyle S (2010) ARRDC3 suppresses breast cancer progression by negatively regulating integrin beta4. Oncogene 29(36):5032–5047. doi:10.1038/onc.2010.250
34. Adelaide J, Finetti P, Bekhouche I, Repellini L, Geneix J, Sircoulomb F, Charafe-Jauffret E, Cervera N, Desplans J, Parzy D, Schoenmakers E, Viens P, Jacquemier J, Birnbaum D, Bertucci F, Chaffanet M (2007) Integrated profiling of basal and luminal breast cancers. Cancer Res 67(24):11565–11575. doi:10.1158/0008-5472.can-07-2536