Am J Cancer Res 2015;5(5):1854-1861
www.ajcr.us /ISSN:2156-6976/ajcr0006809

Original Article

FGFR2 gene polymorphisms are associated with breast cancer risk in the Han Chinese population

Peng Xia[1,2,3], Bin Li[4], Tingting Geng[3,5], Zhiping Deng[1], Chengxue Dang[1], Dongmin Chang[1], Longli Kang[6,7], Tianbo Jin[2,3,5], Chao Chen[2,3]

[1]Department of Oncology, First Affiliated Hospital, Xi'an Jiaotong University, Xi'an 710061, China; [2]School of Life Sciences, Northwest University, Xi'an 710069, China; [3]National Engineering Research Center for Miniaturized Detection Systems, Xi'an 710069, China; [4]Department of Oncology, First Affiliated Hospital, Xi'an Medical College, Xi'an 710077, China; [5]Department of endocrinology, First Affiliated Hospital, Xi'an Jiaotong University, Xi'an 710069, China; [6]Key Laboratory of High Altitude Environment and Genes Related to Diseases of Tibet Autonomous Region, School of Medicine, Xizang Minzu University, Xianyang, 712082, China; [7]Department of Genetics, Yale University School of Medicine, New Haven, CT 06520 USA

Received February 6, 2015; Accepted April 10, 2015; Epub April 15, 2015; Published May 1, 2015

Abstract: Aims and background: Breast cancer is one of the most common neoplasms among women in many developing countries including China, and is the leading cause of female cancer-related deaths worldwide. Methods: In the current study, we analyzed the relationship between 14 tag single-nucleotide polymorphisms (tSNPs) and breast cancer risk in the Han Chinese population including 185 breast cancer patients and 199 healthy women controls on the different types of breast cancer and menopausal status. Results: Overall, we found rs2981579 in the *FGFR2* gene, and rs2380205 were associated with breast cancer susceptibility. Conclusions: These findings indicate that *FGFR2* was associated with breast cancer risk in the Han Chinese population, support the hypothesis that the applicability of a common susceptibility locus must be confirmed among genetically different populations.

Keywords: Single nucleotide polymorphism (SNP), breast cancer, *FGFR2*, case-control studies

Introduction

Breast cancer is one of the most common malignancies in women worldwide. In the past 10 years, the incidence of breast cancer rose by 20-30% among China's urban registries [1]. With an investigation of 32,798,187 breast cancer from 41 registries in 2008 in China [2], breast cancer has become the leading cause of cancer-related deaths in women.

Breast cancer is a complex disease, and may be caused by combination of genetic, environmental, and behavioral factors [3, 4]. Genome-wide association studies (GWAS) have reported some susceptibility variants [5-8]. Among these variants, fourteen sites have been researched in Chinese. However, the results in Chinese were inconsistent with across studies. The aim of this study was to examine the association between the 14 SNPs and breast cancer risk in the Xi'an Han Chinese. To investigate potential relationships between gene single nucleotide polymorphisms (SNPs) and the susceptibility of breast cancer, we performed a comprehensive association analysis in a case-control study and a stratified analysis by menopausal status and analysis of cancer subtype in the Han Chinese population.

Materials and methods

Study participants

Two hundred breast cancer patients recently diagnosed and 200 unrelated healthy women at the First Affiliated Hospital, Xi'an Jiaotong University from December 2011 to October 2012 in Xi'an, China were included in this study. All participants were ≥ 18 years and living in Xi'an city or nearby areas.

Fifteen cases were excluded due to unclear clinical information. Finally, we successfully genotyped 185 breast cancer cases. All controls were healthy without any diseases related to vital organs. We evaluated α-fetoprotein and plasma carcinoembryonic antigen to ensure the quality of the controls. Finally, we selected 199 unrelated healthy subjects to further analysis.

Table 1. Characteristics of breast cancer patients and controls

	Patients (n = 185)	Controls (n = 199)	*p*
Age (years)	46.5 ± 9.4	45.4 ± 6.9	0.209[a]
25-40 years	57 (30.8%)	57 (28.6%)	
41-55 years	95 (51.4%)	130 (65.3%)	
> 55 years	33 (17.8%)	12 (6.1%)	
BMI (kg/m2)	23.1±3.0	22.5 ± 2.5	0.038*,[a]
Sex			
Women	185 (100%)	199 (100%)	
Menopausal state			
Premenopausal	115 (62.2%)	121 (60.8%)	0.785[b]
Postmenopausal	70 (37.8%)	78 (39.2%)	
Tumor size (cm)			
≤ 2.0	41 (22.2%)		
> 2.0	144 (77.8%)		
Histology			
DIC	166 (89.7%)		
LIC	5 (2.7%)		
Others	14 (7.6%)		
Clinical stages			
Grades 1-2	137 (74.1%)		
Grades 3-4	48 (25.9%)		
Lymph node metastasis			
Node-negative	107 (57.8%)		
Node-positive	78 (42.2%)		

[a]*p* values were calculated using Student's t-tests. [b]*p* values were calculated from two-sided chi-square tests. *$p \leq 0.05$ indicates statistical significance.

Clinical data and demographic information

We used a standardized epidemiological questionnaire to collect demographic and personal data. The use of human blood sample and the protocol in this study were strictly conformed to the principles expressed in the Declaration of Helsinki and were approved by the institutional ethical committees of the First Affiliated Hospital, Xi'an Jiaotong University. We also obtained signed informed consent from each participant.

SNP selection and gen otyping

Fourteen tSNPs with minor allele frequencies (MAF) >5% in the Chinese Han Beijing population were successfully genotyped. The GoldMag® nanoparticles method (GoldMag Co. Ltd., Xi'an City, China) was used to extract genomic DNA. We used Sequenom MassARRAY Assay (Sequenom Co. Ltd., San Diego, California, USA) platform to design Multiplexed SNP MassEXTEND assays [9], genotyped SNP, and data management and analyses [10].

Statistical analyses

Fisher's exact test and χ^2 tests were used to evaluate departure from Hardy-Weinberg equilibrium (HWE) in control subjects and calculate the difference in tSNP allele distribution between cases and controls, respectively [11]. $p = 0.05$ was used as the threshold of statistical significance. Associations between the selected SNPs and the risk of breast cancer were assessed using genotypic model analysis (co-dominant, dominant, recessive, over-dominant, and log-additive) by unconditional logistic regression analysis adjusted for age and gender age, menopausal state and body mass index [12].

In stratified analysis by menopausal status, we used ordinal variables coded as the number of variant alleles, 0, 1 or 2, assuming a log-additive genetic model to increase the statistical power. To test for interaction between SNP's and menopausal status, we computed p values from a one degree of freedom likelihood ratio test comparing logistic regression models with and without the interaction term.

In analysis of tumor subtype, we examined associations separately for women with different ER and/or PR status, each compared to all controls. Effect heterogeneity by ER and/or PR status was tested using Cochran-Armitage trend test based on case-case study.

The association of SNPs genotype with breast cancer risk was tested using SNPStats software (http://bioinfo.iconcologia.net/snpstats/start.htm) [13].

Results

The distribution of selected cases and controls characteristics are shown in **Table 1**. The body mass index (BMI) was significantly different between breast cancer patients and healthy controls ($p = 0.038$). We found a correlation between rs2380205 and increased breast cancer susceptibility (OR = 1.79, 95% CI, 1.13-2.83; $p = 0.012$) using χ^2 test. Moreover,

Table 2. Basic information of candidate SNPs

SNP ID	Gene Name	Allele (A/B)	Chromosome position	MAF		HWE *p*	ORs	95% CI		*p*
				Case	Control					
rs11249433	LOC647121	C/T	chr1: 121280613	0.019	0.033	0.892	0.57	0.23	1.46	0.238
rs2981579	FGFR2	C/T	chr10: 123337335	0.431	0.480	0.706	0.82	0.62	1.10	0.180
rs1219648	FGFR2	G/A	chr10: 123346190	0.494	0.452	0.998	1.19	0.89	1.58	0.139
rs10510102	ATE1	G/A	chr10: 123625190	0.157	0.206	0.766	0.72	0.49	1.04	0.081
rs2380205		T/C	chr10: 5886734	0.144	0.086	0.915	1.79	1.13	2.83	0.012*
rs10822013	ZNF365	T/C	chr10: 64251977	0.489	0.447	0.888	1.19	0.89	1.58	0.245
rs10995190	ZNF365	A/G	chr10: 64278682	0.022	0.005	0.997	4.40	0.93	20.88	0.086
rs704010	ZMIZ1	A/G	chr10: 80841148	0.343	0.302	0.010#	1.21	0.89	1.64	0.223
rs3817198	LSP1	C/T	chr11: 1909006	0.119	0.145	0.474	0.80	0.52	1.22	0.294
rs614367		T/C	chr11: 69328764	0.019	0.005	0.997	3.86	0.80	18.73	0.071
rs999737	RAD51L1	T/C	chr14: 69034682	0.003	0.005	0.997	0.54	0.05	5.98	0.610
rs3803662	TOX3	C/T	chr16: 52586341	0.315	0.334	0.795	0.92	0.67	1.24	0.573
rs3112612	LOC643714	C/T	chr16: 52635164	0.255	0.216	0.997	1.25	0.89	1.75	0.197
rs4973768	SLC4A7	T/C	chr3: 27416013	0.261	0.234	0.882	1.16	0.83	1.61	0.380

#site with HWE $p \leq 0.01$ is excluded; *p value ≤ 0.05 indicates statistical significance; Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; OR, odd ratio; CI, confidence interval; A/B stands for minor/major alleles on the control sample frequencies.

Table 3. Relationship between rs2380205, rs2981579 and breast cancer risk (age adjusted)

SNP ID	Model	Genotype	Control	Case	Without adjustment		With adjustment	
					OR (95% CI)	*p*-value[a]	OR (95% CI)	*p*-value[b]
rs2380205	Codominant	C/C	164 (83.2%)	132 (73.3%)	1.00	0.039	1.00	0.055
		T/C	32 (16.2%)	44 (24.4%)	1.69 (1.02-2.82)		1.69 (1.02-2.82)	
		T/T	1 (0.5%)	4 (2.2%)	5.19 (0.57-47.34)		5.19 (0.57-47.34)	
	Dominant	C/C	164 (83.2%)	132 (73.3%)	1.00	0.021	1.00	0.034*
		T/C-T/T	33 (16.8%)	48 (26.7%)	1.80 (1.09-2.96)		1.72 (1.04-2.86)	
	Recessive	C/C-T/C	196 (99.5%)	176 (97.8%)	1.00	0.120	1.00	0.120
		T/T	1 (0.5%)	4 (2.2%)	4.68 (0.51-42.49)		4.99 (0.53-47.41)	
	Over-dominant	C/C-T/T	165 (83.8%)	136 (75.6%)	1.00	0.052	1.00	0.082
		T/C	32 (16.2%)	44 (24.4%)	1.65 (0.99-2.75)		1.58 (0.94-2.65)	
	Log-additive	---	---	---	1.79 (1.12-2.84)	0.012*	1.73 (1.08-2.76)	0.020*
rs2981579	Codominant	T/T	56 (28.6%)	55 (30.4%)	1.00	0.120	1	0.120
		C/T	92 (46.9%)	96 (53%)	1.07 (0.67-1.71)		1.09 (0.68-1.76)	
		C/C	48 (24.5%)	30 (16.6%)	0.62 (0.34-1.12)		0.62 (0.34-1.13)	
	Dominant	T/T	56 (28.6%)	55 (30.4%)	1.00	0.690	1	0.740
		C/T-C/C	140 (71.4%)	126 (69.6%)	0.91 (0.59-1.42)		0.93 (0.59-1.45)	
	Recessive	T/T-C/T	148 (75.5%)	151 (83.4%)	1.00	0.043*	1	0.042*
		C/C	48 (24.5%)	30 (16.6%)	0.59 (0.35-0.99)		0.59 (0.35-0.99)	
	Over-dominant	T/T-C/C	104 (53.1%)	85 (47%)	1.00	0.210	1	0.180
		C/T	92 (46.9%)	96 (53%)	1.30 (0.87-1.95)		1.33 (0.88-2.00)	
	Log-additive	---	---	---	0.81 (0.61-1.08)	0.160	0.81 (0.61-1.09)	0.170

*p value ≤ 0.05 indicates statistical significance; Abbreviations: OR, odd ratio; CI, confidence interval; p^a: p values were calculated from two-sided chi-square tests or Fisher's exact tests for either genotype distribution. p^b: p values were calculated by unconditional logistic regression adjusted for age, menopausal state and body mass index.

rs2380205 remained significant after further adjustment (p = 0.020). One tSNP, rs704010, was excluded for further analysis since it derived from HWE at 1% p level (**Table 2**).

Table 4. Haplotype association with response (age-adjusted)

	rs10510102	rs1219648	rs2981579	Freq	OR (95% CI)	*p*-value
1	A	G	T	0.4065	1.00	---
2	A	A	C	0.3519	0.83 (0.58-1.19)	0.31
3	G	A	C	0.1022	0.57 (0.34-0.97)	0.037*
4	G	G	T	0.0655	0.75 (0.34-1.67)	0.48
5	A	A	T	0.0554	0.68 (0.32-1.43)	0.31
6	G	A	T	0.0143	0.99 (0.17-5.70)	0.99
rare	*	*	*	0.0042	0.48 (0.04-5.76)	0.57

**p* value ≤ 0.05 indicates statistical significance; Abbreviations: OR, odds ratio; CI, confidence interval.

Table 5. Odds ratios for breast cancer risk by menopausal status

ID	Premenopausal		Postmenopausal		Phet
	OR	*p*-value	OR	*p*-value	
rs11249433	0.33 (0.09-1.27)	0.107	0.92 (0.21-4.12)	0.916	0.265
rs4973768	1.23 (0.82-1.86)	0.312	0.83 (0.45-1.54)	0.560	0.416
rs2380205	2.40 (1.29-4.45)	0.005	1.01 (0.47-2.19)	0.974	0.107
rs10822013	1.22 (0.840-1.77)	0.298	0.92 (0.57-1.50)	0.743	0.544
rs10995190	/	0.999	1.13 (0.15-8.61)	0.906	0.031
rs704010	1.05 (0.70-1.57)	0.827	1.74 (0.97-3.15)	0.065	0.146
rs2981579	0.80 (0.54-1.15)	0.223	0.85 (0.53-1.36)	0.503	0.758
rs1219648	1.35 (0.92-1.99)	0.124	1.22 (0.75-1.97)	0.422	0.627
rs10510102	0.63 (0.40-1.00)	0.045	0.89 (0.46-1.69)	0.713	0.296
rs3817198	0.93 (0.54-1.61)	0.803	0.55 (0.27-1.15)	0.111	0.316
rs614367	2.87 (0.54-15.28)	0.216	/	0.999	0.323
rs999737	0.99 (0.06-16.15)	0.995	/	0.999	0.337
rs3803662	0.87 (0.59-1.28)	0.466	0.96 (0.57-1.60)	0.866	0.729
rs3112612	1.42 (0.91-2.19)	0.121	0.98 (0.57-1.69)	0.949	0.309

p value ≤ 0.05 indicates statistical significance OR, odd ratio; CI, confidence interval.

We further used SNPStats software to analyze the associations between tSNPs and breast cancer risk. In the log-additive model, allele "T" of rs2380205 increased breast cancer risk by 1.79-fold (OR = 1.79, 95% CI, 1.12-2.84; p = 0.012). In the recessive model, we found that genotype "CC" of rs2981579 in *FGFR2* decreased breast cancer risk by 0.59-fold (OR = 0.59, 95% CI, 0.35-0.99; p = 0.043) (**Table 3**).

The relationship between *FGFR2-ATE1* haplotypes and breast cancer risk are listed in **Table 4**. Haplotype "GAC" in the *FGFR2-ATE1* gene was found to decrease the risk of breast cancer (OR = 0.57, 95% CI, 0.34-0.97; p = 0.037).

Results of the study of the association between gene polymorphism and breast cancer risk, evaluated by menopausal status, are shown in **Table 5**. Stratification by menopausal status revealed that the risk of breast cancer was significantly elevated for the minor allele (T) of rs2380205 among premenopausal women (OR = 2.40, 95% CI, 1.29-4.45) in log-additive genetic model. The minor allele (G) of rs10510102 of risk was slight lower among premenopausal women (OR = 0.63, 95% CI, 0.40-1.00) than among postmenopausal women (OR = 0.89, 95% CI 0.46-1.69). However, there was considerable overlap in CIs, which were wide due to small numbers of women in each genotype-exposure category.

As show **Table 6**, when the cases were divided into subgroups by ER/PR status, the effects the minor allele (C) of rs3112612 was more evident for the ER/PR cases in log-additive genetic model. However, the effects of other genotypes were not different by ER/PR status. The minor allele (C) of rs3112612 shows significantly stronger association with risk of ER-negative tumors, PR negative tumors, ER/PR negative tumors respectively (OR = 1.97, 95% CI, 1.22-3.17; OR = 1.80, 95% CI, 1.149-2.81; OR = 2.08, 95% CI, 1.25-3.46) in log-additive genetic model.

Discussion

Fibroblast growth factor receptor 2 (*FGFR2*) is a member of the fibroblast growth receptor family. The extracellular portion of the protein interacts with fibroblast growth factors, initiating a cascade of downstream signals, ultimately influencing mitogenesis and differentiation [14]. Rs2981579 in the *FGFR2* have been

Table 6. Breast cancer risks among subgroups of cases by ER and PR status

ID	ER			PR			ER/PR		
	+	-	Phet	+	-	Phet	+	-	Phet
rs11249433	0.59 (0.20-1.71)	0.48 (0.10-2.25)	0.801	0.67 (0.23-1.96)	0.38 (0.08-1.78)	0.507	2.15 (0.26-2.15)	0.57 (0.12-2.66)	0.756
rs4973768	1.10 (0.76-1.59)	1.12 (0.69-1.81)	0.663	1.13 (0.77-1.66)	1.09 (0.70-1.70)	0.877	1.68 (0.76-1.68)	1.17 (0.71-1.93)	0.820
rs2380205	1.87 (1.11-3.13)	1.52 (0.78-2.94)	0.673	1.82 (1.05-3.13)	1.72 (0.95-3.12)	0.909	2.98 (0.97-2.98)	1.31 (0.64-2.67)	0.607
rs10822013	1.07 (0.77-1.49)	1.22 (0.80-1.85)	0.322	1.04 (0.74-1.48)	1.21 (0.82-1.78)	0.309	1.49 (0.74-1.49)	1.25 (0.80-1.95)	0.264
rs10995190	4.11 (0.77-22.00)	6.71 (0.99-45.44)	0.780	5.76 (1.12-29.55)	3.48 (0.44-27.5)	0.356	27.01 (0.95-27.01)	5.47 (0.68-44.36)	0.756
rs704010	1.25 (0.86-1.81)	1.16 (0.71-1.89)	0.775	1.20 (0.80-1.79)	1.25 (0.81-1.92)	0.623	1.78 (0.79-1.78)	1.14 (0.68-1.90)	1.000
rs2981579	0.83 (0.60-1.15)	0.78 (0.52-1.19)	0.972	0.81 (0.58-1.14)	0.83 (0.57-1.21)	0.960	1.18 (0.59-1.18)	0.83 (0.54-1.29)	0.905
rs1219648	1.36 (0.97-1.90)	1.21 (0.80-1.84)	0.390	1.24 (0.88-1.77)	1.37 (0.93-2.01)	0.624	1.84 (0.89-1.84)	1.26 (0.80-1.97)	0.792
rs10510102	0.65 (0.43-1.00)	0.82 (0.49-1.39)	0.349	0.70 (0.45-1.09)	0.71 (0.43-1.18)	0.818	1.01 (0.40-1.01)	0.72 (0.40-1.29)	0.568
rs3817198	0.64 (0.38-1.08)	0.99 (0.55-1.77)	0.183	0.69 (0.404-1.18)	0.85 (0.49-1.50)	0.441	1.12 (0.36-1.12)	0.95 (0.51-1.79)	0.253
rs614367	3.93 (0.74-20.86)	5.35 (0.66-43.42)	0.793	4.46 (0.836-23.75)	3.75 (0.48-29.52)	0.499	26.10 (0.93-26.10)	5.64 (0.70-45.35)	0.747
rs999737	0.79 (0.07-8.84)	/	0.482	0.90 (0.08-10.10)	/	0.407	10.91 (0.09-10.91)	/	0.471
rs3803662	0.80 (0.56-1.14)	1.14 (0.74-1.75)	0.131	0.76 (0.53-1.10)	1.13 (0.761-1.69)	0.051	1.05 (0.49-1.05)	1.10 (0.70-1.75)	0.075
rs3112612	0.98 (0.66-1.44)	1.97 (1.22-3.17)	0.010	0.95 (0.63-1.41)	1.80 (1.149-2.81)	0.016	1.40 (0.61-1.40)	2.08 (1.25-3.46)	0.006

p value ≤ 0.05 indicates statistical significance.

reported to associate with risk of sporadic postmenopausal breast cancer in European women [15]. In addition, our result showed rs2981579 that are associated with breast cancer in the Han Chinese population. These evidences both indicate that *FGFR2* polymorphisms may have important implications in breast cancer carcinogenesis.

The SNP rs2380205 lies in a 105-kb block on chromosome 10p15, which contains the genes ANKRD16 and FBXO18 [16]. In our study, we identified rs2380205 of Han Chinese living in Xi'an (northwest of China) was associated with an increased risk of breast cancer. However, in a large scale case-control study in Nanjing (east of China), no significant association was observed between rs2380205 and breast cancer risk [17]. Taken together, these results indicate a contradiction for chromosome 10p15 in breast cancer risk; therefore, whether this SNP has breast susceptibility warrants further study.

Our study shows that differ according to ER and PR status breast cancer risk are different. A number of studies suggested the different relationship between risk factors such as age, body mass index smoking of breast cancer, and breast cancer by ER and PR status [18-21]. It is known that patients who have ER^- or PR^- receptors tend to have a poor prognosis than patients with these receptors and the hormone receptor status has a profound effect on therapeutic decisions. Colditz et al. [18] have concluded that the incidence rates and risk factors for breast cancer differ according to ER and PR status and that breast cancer risk should be estimated according to the ER and PR status. However, other studies did not find any significant differences in the profile of risk factors by breast cancer subtypes [22, 23]. Although the underlying biological mechanisms still remain to be investigated, examining potentially modifiable breast cancer risk factors by tumor ER and PR status may provide us greater insight into breast cancer etiology and the mechanisms underlying the risk of associations [24].

In our study we sought to determine whether these loci polymorphisms are associated with breast cancer risk may be modified by menopausal status. Although the mechanisms are not elucidated, these data suggest that there may be an interaction between the gene polymorphism and menopausal status in breast cancer risk. This further supports arguments from a number of studies suggesting that breast cancer etiology may differ between premenopausal and postmenopausal women, warranting the careful classification and separation of women by menopausal status in studies of breast cancer risk factors.

Here, we identified for the first time one risk tSNP on 10p15 (rs2380205) and one protective tSNPs in *FGFR2* (rs2981579) that are associated with breast cancer in the Han Chinese population. In stratified analysis we need to further larger sample studies, gene-environment and gene-gene interaction in breast cancer development.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81102026), China Postdoctoral Science Foundation funded project (No. 2013M532078) and the Science and technology project of Shaanxi Province (No. S2011SF1851). We thanked BioScience Writers for assistant in the preparation of this manuscript.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Tianbo Jin and Chao Chen, School of Life Sciences, Northwest University, Xi'an 710069, China. Tel: +86-29-88302831; Fax: +86-29-88303551; E-mail: tianbojin1973@163.com (TBJ); Tel: +86-29-88303800; Fax: +86-29-88303800; E-mail: chaochenxd898@gmail.com (CC)

References

[1] Porter P. "Westernizing" women's risks? Breast cancer in lower-income countries. N Engl J Med 2008; 358: 213-216.

[2] Chen J, Jiang Y, Liu X, Qin Z, Dai J, Jin G, Ma H, Wang S, Wang X, Hu Z and Shen H. Genetic variants at chromosome 9p21, 10p15 and 10q22 and breast cancer susceptibility in a Chinese population. Breast Cancer Res Treat 2012; 132: 741-6.

[3] Nathanson KL, Wooster R, Weber BL. Breast cancer genetics: What we know and what we need. Nat Med 2001; 7: 552-6.

[4] Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC. Linkage of Early-

Onset Familial Breast Cancer to Chromosome 17q21. Science 1990; 250: 1684-9.

[5] Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, Schmidt MK, Chang-Claude J, Bojesen SE, Bolla MK, Wang Q, Dicks E, Lee A, Turnbull C, Rahman N, Breast, Ovarian Cancer Susceptibility C, Fletcher O, Peto J, Gibson L, Dos Santos Silva I, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Czene K, Irwanto A, Liu J, Waisfisz Q, Meijers-Heijboer H, Adank M, Hereditary B; Ovarian Cancer Research Group N, van der Luijt RB, Hein R, Dahmen N, Beckman L, Meindl A, Schmutzler RK, Muller-Myhsok B, Lichtner P, Hopper JL, Southey MC, Makalic E, Schmidt DF, Uitterlinden AG, Hofman A, Hunter DJ, Chanock SJ, Vincent D, Bacot F, Tessier DC, Canisius S, Wessels LF, Haiman CA, Shah M, Luben R, Brown J, Luccarini C, Schoof N, Humphreys K, Li J, Nordestgaard BG, Nielsen SF, Flyger H, Couch FJ, Wang X, Vachon C, Stevens KN, Lambrechts D, Moisse M, Paridaens R, Christiaens MR, Rudolph A, Nickels S, Flesch-Janys D, Johnson N, Aitken Z, Aaltonen K, Heikkinen T, Broeks A, Veer LJ, van der Schoot CE, Guenel P, Truong T, Laurent-Puig P, Menegaux F, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Zamora MP, Perez JI, Pita G, Alonso MR, Cox A, Brock IW, Cross SS, Reed MW, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Henderson BE, Schumacher F, Le Marchand L, Andrulis IL, Knight JA, Glendon G, Mulligan AM, kConFab I, Australian Ovarian Cancer Study G, Lindblom A, Margolin S, Hooning MJ, Hollestelle A, van den Ouweland AM, Jager A, Bui QM, Stone J, Dite GS, Apicella C, Tsimiklis H, Giles GG, Severi G, Baglietto L, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Brenner H, Muller H, Arndt V, Stegmaier C, Swerdlow A, Ashworth A, Orr N, Jones M, Figueroa J, Lissowska J, Brinton L, Goldberg MS, Labreche F, Dumont M, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Bruning T, Network G, Radice P, Peterlongo P, Manoukian S, Bonanni B, Devilee P, Tollenaar RA, Seynaeve C, van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Durda K, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Bogdanova NV, Antonenkova NN, Dork T, Kristensen VN, Anton-Culver H, Slager S, Toland AE, Edge S, Fostira F, Kang D, Yoo KY, Noh DY, Matsuo K, Ito H, Iwata H, Sueta A, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Shu XO, Lu W, Gao YT, Cai H, Teo SH, Yip CH, Phuah SY, Cornes BK, Hartman M, Miao H, Lim WY, Sng JH, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Shen CY, Hsiung CN, Wu PE, Ding SL, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Blot WJ, Signorello LB, Cai Q, Zheng W, Deming-Halverson S, Shrubsole M, Long J, Simard J, Garcia-Closas M, Pharoah PD, Chenevix-Trench G, Dunning AM, Benitez J and Easton DF. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013; 45: 353-361, 361e1-2.

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

[7] Thomas G, Jacobs KB, Kraft P, Yeager M, Wacholder S, Cox DG, Hankinson SE, Hutchinson A, Wang Z, Yu K, Chatterjee N, Garcia-Closas M, Gonzalez-Bosquet J, Prokunina-Olsson L, Orr N, Willett WC, Colditz GA, Ziegler RG, Berg CD, Buys SS, McCarty CA, Feigelson HS, Calle EE, Thun MJ, Diver R, Prentice R, Jackson R, Kooperberg C, Chlebowski R, Lissowska J, Peplonska B, Brinton LA, Sigurdson A, Doody M, Bhatti P, Alexander BH, Buring J, Lee IM, Vatten LJ, Hveem K, Kumle M, Hayes RB, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover RN, Chanock SJ and Hunter DJ. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). Nat Genet 2009; 41: 579-584.

[8] Fletcher O, Johnson N, Orr N, Hosking FJ, Gibson LJ, Walker K, Zelenika D, Gut I, Heath S, Palles C, Coupland B, Broderick P, Schoemaker M, Jones M, Williamson J, Chilcott-Burns S, Tomczyk K, Simpson G, Jacobs KB, Chanock SJ, Hunter DJ, Tomlinson IP, Swerdlow A, Ash-

worth A, Ross G, dos Santos Silva I, Lathrop M, Houlston RS and Peto J. Novel breast cancer susceptibility locus at 9q31.2: results of a genome-wide association study. J Natl Cancer Inst 2011; 103: 425-435.

[9] Gabriel S, Ziaugra L and Tabbaa D. SNP Genotyping Using the Sequenom MassARRAY iPLEX Platform. Curr Protoc Hum Genet 2009.

[10] Thomas RK, Baker AC, Debiasi RM, Winckler W, Laframboise T, Lin WM, Wang M, Feng W, Zander T, MacConaill L, Lee JC, Nicoletti R, Hatton C, Goyette M, Girard L, Majmudar K, Ziaugra L, Wong KK, Gabriel S, Beroukhim R, Peyton M, Barretina J, Dutt A, Emery C, Greulich H, Shah K, Sasaki H, Gazdar A, Minna J, Armstrong SA, Mellinghoff IK, Hodi FS, Dranoff G, Mischel PS, Cloughesy TF, Nelson SF, Liau LM, Mertz K, Rubin MA, Moch H, Loda M, Catalona W, Fletcher J, Signoretti S, Kaye F, Anderson KC, Demetri GD, Dummer R, Wagner S, Herlyn M, Sellers WR, Meyerson M and Garraway LA. High-throughput oncogene mutation profiling in human cancer. Nat Genet 2007; 39: 347-351.

[11] Adamec C. [EXAMPLE OF THE USE OF THE NONPARAMETRIC TEST. TEST X2 FOR COMPARISON OF 2 INDEPENDENT EXAMPLES]. Cesk Zdrav 1964; 12: 613-619.

[12] Bland JM and Altman DG. Statistics notes. The odds ratio. BMJ 2000; 320: 1468.

[13] Sole X, Guino E, Valls J, Iniesta R and Moreno V. SNPStats: a web tool for the analysis of association studies. Bioinformatics 2006; 22: 1928-1929.

[14] Grose R and Dickson C. Fibroblast growth factor signaling in tumorigenesis. Cytokine Growth Factor Rev 2005; 16: 179-186.

[15] Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, Wacholder S, Wang Z, Welch R, Hutchinson A, Wang J, Yu K, Chatterjee N, Orr N, Willett WC, Colditz GA, Ziegler RG, Berg CD, Buys SS, McCarty CA, Feigelson HS, Calle EE, Thun MJ, Hayes RB, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover RN, Thomas G and Chanock SJ. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 2007; 39: 870-874.

[16] Turnbull C, Ahmed S, Morrison J, Pernet D, Renwick A, Maranian M, Seal S, Ghoussaini M, Hines S, Healey CS, Hughes D, Warren-Perry M, Tapper W, Eccles D, Evans DG, Breast Cancer Susceptibility C, Hooning M, Schutte M, van den Ouweland A, Houlston R, Ross G, Langford C, Pharoah PD, Stratton MR, Dunning AM, Rahman N and Easton DF. Genome-wide association study identifies five new breast cancer susceptibility loci. Nat Genet 2010; 42: 504-507.

[17] Chen J, Jiang Y, Liu X, Qin Z, Dai J, Jin G, Ma H, Wang S, Wang X, Hu Z and Shen H. Genetic variants at chromosome 9p21, 10p15 and 10q22 and breast cancer susceptibility in a Chinese population. Breast Cancer Res Treat 2012; 132: 741-746.

[18] Colditz GA, Rosner BA, Chen WY, Holmes MD and Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst 2004; 96: 218-228.

[19] Cotterchio M, Kreiger N, Theis B, Sloan M and Bahl S. Hormonal factors and the risk of breast cancer according to estrogen- and progesterone-receptor subgroup. Cancer Epidemiol Biomarkers Prev 2003; 12: 1053-1060.

[20] Britton JA, Gammon MD, Schoenberg JB, Stanford JL, Coates RJ, Swanson CA, Potischman N, Malone KE, Brogan DJ, Daling JR and Brinton LA. Risk of breast cancer classified by joint estrogen receptor and progesterone receptor status among women 20-44 years of age. Am J Epidemiol 2002; 156: 507-516.

[21] Manjer J, Malina J, Berglund G, Bondeson L, Garne JP and Janzon L. Smoking associated with hormone receptor negative breast cancer. Int J Cancer 2001; 91: 580-584.

[22] Zhu K, Beiler J, Hunter S, Payne-Wilks K, Roland CL, Forbes DS, Chinchilli VM, Bernard LJ, Jacobsen KH and Levine RS. The relationship between menstrual factors and breast cancer according to estrogen receptor status of tumor: a case-control study in African-American women. Ethn Dis 2002; 12: S3-23-29.

[23] McCredie MR, Dite GS, Southey MC, Venter DJ, Giles GG and Hopper JL. Risk factors for breast cancer in young women by oestrogen receptor and progesterone receptor status. Br J Cancer 2003; 89: 1661-1663.