Research Article

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Common Genetic Variants Associated with Breast Cancer in Korean Women and Differential Susceptibility According to Intrinsic Subtype

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Abstract

Background: Recently identified genetic variants from genome-wide association studies (GWAS) on breast cancer have not been validated in Asian populations, except in China. In this study, we sought to confirm the association between known variants and breast cancer in Korean women and further evaluate the associations of individual single nucleotide polymorphisms (SNP) with different intrinsic subtypes of breast cancer.

Methods: In total, 3,321 invasive breast cancer patients and 3,500 healthy controls were genotyped for five SNPs by using the TaqMan assay. The SNPs genotyped included rs2046210 (6q25.1), rs2981582 (*FGFR2*), rs889312 (*MAP3K1*), rs3803662 (*TOX3/TNRC9*), and rs4973768 (*SLC4A7*). Tumors were classified into four intrinsic subtypes based on estrogen receptor (ER), progesterone receptor, HER2, and Ki67 expression.

Results: All five SNPs were significantly associated with risk of breast cancer in dominant, recessive, and additive models. ORs per risk allele (95% CI) were 1.29 (1.16–1.43), 1.40 (1.18–1.68), 1.22 (1.06–1.41), 1.52 (1.30–1.77), and 1.20 (1.08–1.33) for rs2046210, rs2981582, rs889312, rs3803662, and rs4973768, respectively. A multigene logistic regression risk model was generated with the SNPs. In subtype analysis, all 5 SNPs were associated with the Luminal A subtype. Two SNPs (rs2046210 and rs3803662) were linked to the $ER^{-}HER2^{+}$ subtype, and only rs2046210 SNP was associated with the triple-negative subtype.

Conclusions: The five SNPs from GWAS were significantly associated with breast cancer risk in Korean women. Associations were heterogeneous according to the intrinsic subtype of breast cancer.

Impact: Our result is an important contribution to the literature about genetic susceptibility for breast cancer in nonwhite populations. *Cancer Epidemiol Biomarkers Prev; 20(5); 793–8. ©2011 AACR.*

Introduction

Breast cancer is one of the most common malignancies affecting women worldwide. The recent increase in incidence has made breast cancer one of the most frequently recorded diseases among Korean women since 2001 (1). The age-adjusted death rate because of breast cancer in Korea is also rising, with the most rapid increase in the world from 1985 to 1995 (2).

Genetic factors play an important role in breast cancer development. After completion of the human genome project, single nucleotide polymorphisms (SNP) were highlighted as the key variations leading to genetic differences in breast cancer susceptibility between individuals. However, candidate gene approaches have not been successful in reproducibly identifying the significant SNPs associated with breast cancer. Recent genome-wide association studies (GWAS; ref. 3–8) have led to the detection of multiple and robust genetic susceptibility loci for breast cancer. These are common in the general population, but the relative risk for breast cancer conferred by each locus is low. All documented GWAS to date have been conducted on women of European ancestry, except for 1 Chinese study. Because minor allele frequencies of SNPs are highly variable and the linkage disequilibrium patterns differ between ethnicities, it is important to confirm the effects of the variants identified in GWAS in different ethnic populations.

Breast cancer is a heterogeneous disease in which risk factors are suggested to be differentially associated with the development of distinct tumor subtypes with variable biological and clinical features. Consistent with this theory, there is growing evidence that known breast cancer risk factors vary depending on hormone receptor status (9–11). Recent studies have shown that common genetic variants are differentially associated with estrogen receptor $(ER)^{+}$ or ER^{-} breast cancer, providing further support

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for the hypothesis that ER^+ and ER^- diseases result from different etiologic pathways (6, 7, 12). However, limited information has been obtained on additional heterogeneity of genetic risk factors within ER^+ or ER^- tumors according to the intrinsic breast cancer subtype (13). Genomic studies have established that breast cancer can be divided into 4 major intrinsic subtypes (Luminal A, Luminal B, HER2-enriched, basal-like) that differ significantly in terms of incidence, survival, and response to therapy (14–16). The origins and developmental pathways of these subtypes may be subtype dependent (17).

In the present study, we evaluated Korean breast cancer patients for the 5 SNPs recently identified from 4 European and 1 Chinese GWAS. The associations of all GWAS-identified SNPs with breast cancer were further assessed in relation to the 4 intrinsic subtypes defined by using surrogate immunohistochemistry (IHC) markers.

Materials and Methods

Subjects and samples

Consecutive patients with histologically confirmed primary breast cancer subjected to operative procedures between 2002 and 2009 in Seoul National University Hospital were included for analysis. Patients diagnosed with noninvasive breast cancer (ductal carcinoma *in situ* and lobular carcinoma *in situ*) were excluded. Peripheral venous blood samples were obtained and stored at the time of operation. DNA samples from controls were donated from the genome bank of Korea Centers for Disease Control & Prevention. Control subjects were randomly selected from a population-based cohort of 12,000 health examinees. The Korean Health Examinees Study, which was established in 2004, aims to carry out a follow-up every 2 years for each member. The subjects recruited in 14 hospitals and institutions were from a community adult population under 70 years of age, who had no experience of participating in cohort studies and consented to genetic analysis.

In total, 3,321 breast cancer cases and 3,500 healthy control women were genotyped. The mean ages of cases and controls were 48.5±9.8 (range: 21–82) and 52.6±8.1 (range: 23–79), respectively.

This study was approved by the Institutional Review Board for human research at Seoul National University Hospital. Informed consent was obtained from all patients.

SNP selection

Among the common breast cancer susceptibility alleles established from recent GWAS, we selected 5 SNPs for genotyping, specifically, rs2046210 (6q25.1)(8), rs2981582 (*FGFR2*)(3, 5), rs889312 (*MAP3K1*)(3), rs3803662 (*TOX3/TNRC9*)(3), and rs4973768 (*SLC4A7*; ref. 18; Table 1). SNPs that were previously reported as not significantly associated with breast cancer in Korean and other Asian subpopulations were excluded from analysis.

Genotyping method

Genomic DNA was extracted from peripheral blood leukocytes by using a genomic DNA kit (Qiagen), according to the manufacturer's instructions. SNP genotyping was carried out on an Applied Biosystems 7900HT real-time PCR system (Applied Biosystems). Assay reagents for each SNP were additionally obtained from Applied Biosystems. DNA was genotyped following the manufacturer's protocol. Briefly, the components for the genotyping reactions included 2 μL of 10 ng/nL genomic

Table 1. Genotype frequencies of each SNP among control and case

SNP	Chromosome and genes	Genotype	Control *n* (%)	Case *n* (%)	HWEP
rs2046210	6q25.1 (upstream of *ESR1*)	GG	1,586 (45.4)	1,260 (38.8)	0.82
		AG	1,531 (43.8)	1,565 (48.1)	
		AA	376 (10.8)	426 (13.1)	
rs2981582	10q26.13 (*FGFR2*)	GG	1,751 (50.2)	1,497 (46.3)	0.36
		AG	1,457 (41.8)	1,393 (43.1)	
		AA	281 (8.1)	342 (10.6)	
rs889312	5q11.2 (*MAP3K1*)	CC	1,011 (28.9)	1,048 (31.8)	0.87
		CA	1,743 (49.8)	1,628 (49.4)	
		AA	743 (21.2)	620 (18.8)	
rs3803662	16q12.1 (*TOX3/TNRC9*)	AA	1,361 (39.0)	1,481 (45.1)	0.32
		AG	1,617 (46.3)	1,435 (43.7)	
		GG	516 (14.8)	369 (11.2)	
rs4973768	3p24 (*SLC4A7*, *NEK10*)	CC	2,195 (62.8)	1,913 (57.9)	0.51
		CT	1,143 (32.7)	1,213 (36.7)	
		TT	159 (4.5)	177 (5.4)	

HWEP: Hardy–Weinberg equilibrium *P* value

DNA, 2.5 μL of TaqMan Genotyping Master Mix (Applied Biosystems), 0.125 μL of assay mix (40×), and water up to a total volume of 5 μL. The thermocycler conditions were as follows: 50°C for 2 minutes, 95°C for 10 minutes, and 40 cycles of 95°C for 15 seconds and 60°C for 60 seconds. Reactions were analyzed by using Applied Biosystems Sequence Detection Software (Version 2.3).

Intrinsic subtypes

IHC tests were conducted to determine the tumor expression levels of ER, progesterone receptor (PR), HER2, and Ki67. The primary antibodies and dilution factors employed in this study have been described in a previous report (19). IHC tests were carried out on paraffin blocks from tumor tissues fixed in 10% neutral buffered formalin. All IHC tests were carried out in a single laboratory (Seoul National University Hospital) immediately after surgery. Slides were reviewed by a pathologist with no knowledge of the genotype results. We classified ER and PR expression status as positive at a cutoff value of 10% or more positively stained cells per 10 high-power fields. HER2 immunostaining was considered positive when strong (3^+) membranous staining was observed in at least 10% of tumor cells, whereas cases classified as 0 to 1^+ staining were regarded as negative. Cases displaying moderate membranous staining (2^+) were confirmed by using HER2 FISH. At a Ki67 cutoff point of 10% or higher, established by Jung and colleagues (19), tumors were designated "high proliferation." The study population was subgrouped into 4 breast cancer subtypes defined by Hugh and colleagues (20), specifically, triple negative (ER^-negative, PR^-negative, $HER2^-$negative), ER^-HER2^+ (ER^-negative, PR^-negative, $HER2^-$positive), Luminal B (ER^-positive and/or PR^-positive and either $HER2^-$positive and/or $Ki67^{high}$), and Luminal A (ER^-positive and/or PR^-positive and not $HER2^-$positive or $Ki67^{high}$).

Statistical analysis

The chi-square test for genotype distribution was conducted to evaluate deviation from the Hardy–Weinberg equilibrium in each case and control group. Breast cancer risk was estimated as OR and 95% CI, based on unconditional logistic regression adjusted for age (years). Analyses were carried out assuming a dominant, recessive, and additive allelic effect for each polymorphism. The likelihood ratio test was used to examine the effect of each SNP at the 5% significance level.

Stratified analysis according to the 4 breast cancer subtypes was additionally conducted. We calculated OR and 95% CI of SNPs, based on the additive model that assumes a linear increase in disease risk with increasing number of risk alleles.

For the multigene logistic regression risk model, we used the "glm" function in statistical language R (version 2.5.1).

Results

The distribution of all genetic polymorphisms did not deviate from Hardy–Weinberg equilibrium ($P > 0.30$). For rs889312 and rs3803662, the major allele was the risk allele, consistent with the findings of the Chinese study (ref. 21; Table 1).

All 5 breast cancer-associated SNPs identified in previous GWAS (rs2046210, rs4973768, rs2981582, rs3803662, and rs889312) were significantly associated with breast cancer risk in dominant, recessive, and additive models, except rs4973768 in the recessive model (Table 2). OR values ranged from 1.13 (rs889312 in the dominant model) to 1.52 (rs3803662 in the additive model).

Next, we generated a multigene logistic regression risk model with the 5 SNPs. The variables and coefficients are presented in Table 3. The odds of breast cancer determined from this model varied from 0.43 for subjects homozygous (2 copies) for protective variants at all 5 markers [exp $(-0.8334307) = 0.43$] to 2.36 for subjects homozygous for risk variants at all markers [exp $(-0.8334307 + 0.3771801 + 0.3679599 + 0.2210641 + 0.4376367 + 0.2914944) = 2.36$].

According to the intrinsic subtype classification system specified in Materials and Methods, 1685 breast cancer cases were subgrouped as Luminal A, 650 as Luminal B, 310 as ER^-HER2^+, and 574 as triple-negative subtype. In 112 cases, the subtype could not be determined owing to the absence of 1 or more individual marker data. As shown in Figure 1, all 5 SNPs were significantly associated with the Luminal A subtype, and 4 out of 5 SNPs with the Luminal B subtype. Three SNPs, rs2981582 (*FGFR2*), rs889312 (*MAP3K1*), and rs4973768 (*SLC4A7*) showed stronger associations with ER^+ than ER^- tumors. The most remarkable pattern of subtype association was observed with the SNP in 6q25.1 (rs2046210). ORs of this SNP were higher in the Luminal B, ER^-HER2^+, and triple-negative subtypes, compared with the Luminal A subtype. Notably, this was the only significant SNP associated with the triple-negative subtype. On the other hand, the SNP in *TOX3*/*TNRC9* (rs3803662) was significantly linked to the ER^-HER2^+ but not triple-negative subtype of breast cancer.

Discussion

In this large case-control study involving 6,821 participants, we showed that the 5 SNPs identified in GWAS conducted on women of mainly European ancestry were also significantly associated with breast cancer susceptibility in Korean women. This is the second Asian study (21, 22) to validate earlier GWAS results in a large population. The information obtained would be useful for classifying Korean women into the relevant genetic risk groups.

This type of ethnicity-specific study is important, because allele frequencies of SNPs vary among populations

Table 2. Associations between the 5 polymorphisms and breast cancer risk

	Dominant model		Recessive model		Additive model		Homozygote wild-type versus homozygote variant	
	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*
rs2046210	1.31 (1.19–1.45)	7.91×10^{-8}	1.25 (1.07–1.45)	4.57×10^{-3}	1.29 (1.16–1.43)	2.37×10^{-6}	1.42 (1.21–1.67)	1.84×10^{-5}
rs2981582	1.15 (1.04–1.27)	4.70×10^{-3}	1.34 (1.13–1.59)	7.88×10^{-4}	1.40 (1.18–1.68)	1.81×10^{-4}	1.40 (1.18–1.68)	1.81×10^{-4}
rs889312	1.13 (1.02–1.26)	2.25×10^{-2}	1.15 (1.02–1.31)	2.14×10^{-2}	1.22 (1.06–1.41)	5.16×10^{-3}	1.22 (1.06–1.41)	5.27×10^{-3}
rs3803662	1.27 (1.15–1.41)	1.98×10^{-6}	1.37 (1.18–1.59)	2.44×10^{-5}	1.52 (1.30–1.77)	2.03×10^{-7}	1.52 (1.30–1.77)	2.08×10^{-7}
rs4973768	1.20 (1.09–1.33)	2.76×10^{-4}	1.19 (0.94–1.49)	1.33×10^{-1}	1.20 (1.08–1.33)	8.11×10^{-4}	1.27 (1.01–1.60)	4.21×10^{-2}

[a]Adjusted for age.

Table 3. Variables and coefficients of the multigene logistic regression risk model

Variables	Coefficient	Standard error
(Intercept)	−0.8334307	0.09603210
rs2046210 (AG)	0.2688592	0.05282297
rs2046210 (AA)	0.3771801	0.08115160
rs2981582 (AG)	0.1247290	0.05203057
rs2981582 (AA)	0.3679599	0.08905035
rs889312 (CA)	0.1178304	0.06562798
rs889312 (CC)	0.2210641	0.07132804
rs3803662 (AG)	0.2194539	0.07866000
rs3803662 (AA)	0.4376367	0.07915529
rs4973768 (CT)	0.1971477	0.05266590
rs4973768 (TT)	0.2914944	0.11566619

and a positive SNP association with breast cancer in individuals of one ethnicity may be negative in another ethnic population. For example, *CASP8* D302H, which was found to be significantly associated with breast cancer in a large population of Western women (23), was not polymorphic in Korean women (24). Moreover, SNPs in 2q35 (rs13387042; ref. 6), 5p12 (rs10941679; ref. 7), 6q22.33 (rs2180341; ref. 4), and 8q24.21 (rs13281615; ref. 3) identified from GWAS were not associated with breast cancer in Chinese women (21, 22).

We created a multigene logistic regression risk model with the 5 SNPs. The ORs according to percentile (data not shown) were similar to those reported by Pharoah and colleagues (25) calculated by using data from 7 SNPs. On the basis of their results, Pharoah and colleagues recommended that women with higher genetic risk should be subjected to annual screening mammography at a younger age (25). Zheng and colleagues (22) proposed the use of a risk assessment model including both genetic markers and clinical predictors. However, Wacholder and colleagues showed that genetic factors only modestly improved the performance of risk models for breast cancer (26). Thus, there is an urgent need to identify more SNPs to generate a more useful breast cancer risk model composed of common genetic variants (27, 28). Other SNPs from published GWAS should be validated, and large-scale GWAS studies on Korean women are critical.

In our study, rs2981582 (*FGFR2*) and rs889312 (*MAP3K1*) showed stronger associations with ER^+ than ER^- tumors, consistent with data from European studies on susceptibility loci and ER status (6, 7, 12). The *SLC4A7* (rs4973768) variant was also more strongly associated with ER^+ than ER^- tumors, consistent with the Chinese study (21). A large-scale study from the Breast Cancer Association Consortium reported that the *TNRC9/TOX3* (rs3803662) variant was associated with both ER^+ and ER^- subtypes, although the association was slightly weaker for ER^- tumors (12). We observed an association of this SNP with ER^+ as well as the ER^-HER2^+ subtypes, but not the triple-negative subtype.

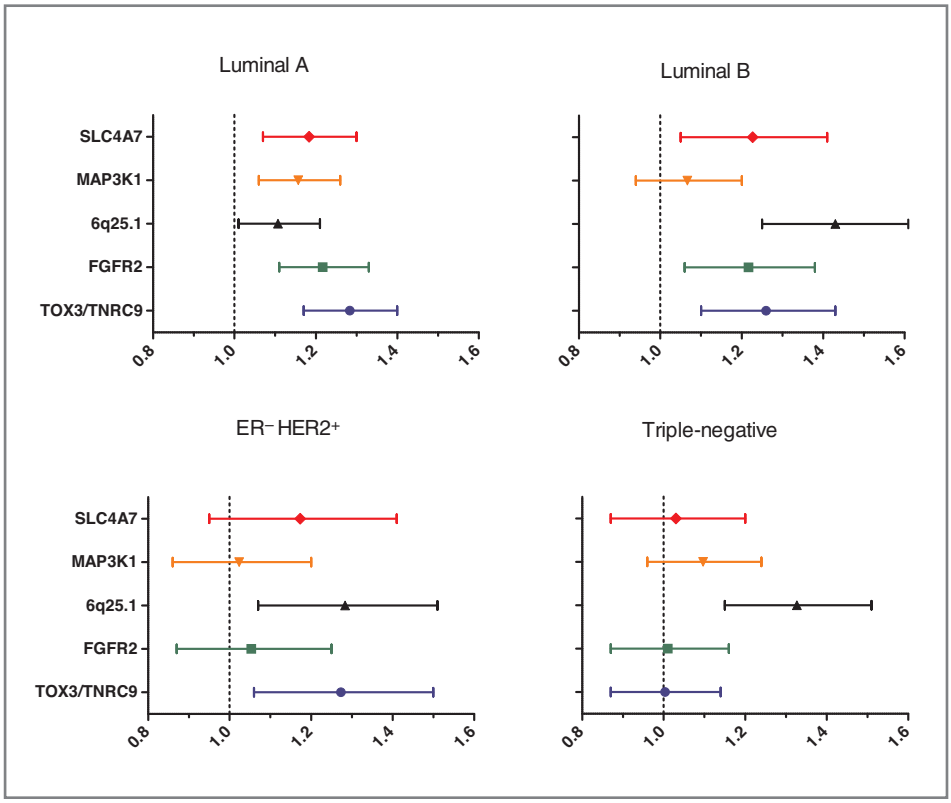

Figure 1. SNP associations are breast cancer subtype specific. *X*-axis: OR adjusted for age. Horizontal bars showing 95% CI.

This further heterogeneity of genetic association within ER^- or ER^+ tumors is a novel finding, and requires further validation in another cohort. Earlier Chinese studies reported a closer association between the variant in rs2046210 (6q25.1) with ER^- than ER^+ tumors (8, 21), which was reconfirmed in our investigation. Furthermore, among the ER^+ tumors, this SNP was associated with the Luminal B subtype as strongly as with ER^- tumors. These findings collectively imply that the associations between SNP and breast cancer are not simply determined on the basis of ER status, but vary according to the intrinsic subtype. Our results are significant, because they support the theory that tumors with different intrinsic subtypes result from different etiologic pathways that have evolved from cancer stem cells (17).

In summary, we have shown that the 5 selected variants identified from earlier GWAS carried out on women of European or Chinese origin are similarly associated with breast cancer in the Korean population. Although the currently identified loci provide low discriminatory accuracy to distinguish between the low- and high-risk groups, combinations of loci established in future studies may be useful in population screening strategies. The finding that SNPs are differentially associated with individual intrinsic subtypes of breast cancer is consistent with the hypothesis that the genetic mechanism of etiology differs between subtypes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. National Cancer Center. Report on the statistics for national cancer incidence 1999–2001. Korea, Goyang-si: National Cancer Center; 2006.
2. Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 2004;6:229–39.
3. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447:1087–93.
4. Gold B, Kirchhoff T, Stefanov S, Lautenberger J, Viale A, Garber J, et al. Genome-wide association study provides evidence for a breast

cancer risk locus at 6q22.33. Proc Natl Acad Sci U S A 2008;105:4340–5.
5. Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 2007;39:870–4.
6. Stacey SN, Manolescu A, Sulem P, Rafnar T, Gudmundsson J, Gudjonsson SA, et al. Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2007;39:865–9.
7. Stacey SN, Manolescu A, Sulem P, Thorlacius S, Gudjonsson SA, Jonsson GF, et al. Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2008;40:703–6.
8. Zheng W, Long J, Gao YT, Li C, Zheng Y, Xiang YB, et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. Nat Genet 2009;41:324–8.
9. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev 2004;13:1558–68.
10. Ma H, Bernstein L, Pike MC, Ursin G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. Breast Cancer Res 2006;8:R43.
11. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 2006;7:910–8.
12. Garcia-Closas M, Hall P, Nevanlinna H, Pooley K, Morrison J, Richesson DA, et al. Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. PLoS Genet 2008;4:e1000054.
13. Garcia-Closas M, Chanock S. Genetic susceptibility loci for breast cancer by estrogen receptor status. Clin Cancer Res 2008;14:8000–9.
14. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006;295:2492–502.
15. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000;406:747–52.
16. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869–74.
17. Prat A, Perou CM. Mammary development meets cancer genomics. Nat Med 2009;15:842–4.
18. Ahmed S, Thomas G, Ghoussaini M, Healey CS, Humphreys MK, Platte R, et al. Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. Nat Genet 2009;41:585–90.
19. Jung SY, Han W, Lee JW, Ko E, Kim E, Yu JH, et al. Ki-67 expression gives additional prognostic information on St. Gallen 2007 and Adjuvant! Online risk categories in early breast cancer. Ann Surg Oncol 2009;16:1112–21.
20. Hugh J, Hanson J, Cheang MC, Nielsen TO, Perou CM, Dumontet C, et al. Breast cancer subtypes and response to docetaxel in node-positive breast cancer: use of an immunohistochemical definition in the BCIRG 001 trial. J Clin Oncol 2009;27:1168–76.
21. Long J, Shu XO, Cai Q, Gao YT, Zheng Y, Li G, et al. Evaluation of breast cancer susceptibility loci in Chinese women. Cancer Epidemiol Biomarkers Prev 2010;19:2357–65.
22. Zheng W, Wen W, Gao YT, Shyr Y, Zheng Y, Long J, et al. Genetic and clinical predictors for breast cancer risk assessment and stratification among Chinese women. J Natl Cancer Inst 2010;102:972–81.
23. Cox A, Dunning AM, Garcia-Closas M, Balasubramanian S, Reed MW, Pooley KA, et al. A common coding variant in CASP8 is associated with breast cancer risk. Nat Genet 2007;39:352–8.
24. Han S, Lee KM, Choi JY, Park SK, Lee JY, Lee JE, et al. CASP8 polymorphisms, estrogen and progesterone receptor status, and breast cancer risk. Breast Cancer Res Treat 2008;110:387–93.
25. Pharoah PD, Antoniou AC, Easton DF, Ponder BA. Polygenes, risk prediction, and targeted prevention of breast cancer. N Engl J Med 2008;358:2796–803.
26. Wacholder S, Hartge P, Prentice R, Garcia-Closas M, Feigelson HS, Diver WR, et al. Performance of common genetic variants in breast-cancer risk models. N Engl J Med 2010;362:986–93.
27. Devilee P, Rookus MA. A tiny step closer to personalized risk prediction for breast cancer. N Engl J Med 2010;362:1043–5.
28. Kraft P, Hunter DJ. Genetic risk prediction–are we there yet?N Engl J Med 2009;360:1701–3.