MEDICAL SCIENCE MONITOR

LAB/IN VITRO RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 3077-3083
DOI: 10.12659/MSM.907422

Received: 2017.10.05
Accepted: 2017.11.09
Published: 2018.05.11

Association of Single-Nucleotide Polymorphisms of CD44 Gene with Susceptibility to Breast Cancer in Chinese Women

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCE 1 Xiao Lin
BCD 2 Xiaojing You
CD 2 Xuezhen Cao
ABCDEF 3 Shenghua Pan

1 Department of Thyroid and Breast Surgery, Ruian People's Hospital of Zhejiang Province, Wenzhou, Zhejiang, P.R. China
2 Department of Tumor Radiotherapy, Ruian People's Hospital of Zhejiang Province, Wenzhou, Zhejiang, P.R. China
3 Department of Pathology, Ruian People's Hospital of Zhejiang Province, Wenzhou, Zhejiang, P.R. China

Corresponding Author: Shenghua Pan, e-mail: panshh108@163.com
Source of support: Departmental sources

Background: This study aimed to evaluate the association of CD44 gene single-nucleotide polymorphisms with susceptibility to breast cancer.

Material/Methods: This case-control study included 242 breast cancer patients and 252 normal people without disease. The single-nucleotide polymorphisms of the CD44 gene in the 2 groups were genotyped by PCR-LDR method. The OR and its 95% CI was calculated by chi-square test and logistic regression analysis. The construction of haplotypes and their interaction analysis with relevant factors were carried out by SHEsis and SNPStats online.

Results: The genotype distribution of CC and CT, CC and CC+CT, and CC+CT and TT in rs13347 showed a significant difference between cases and controls, and the difference in distribution of alleles C and T was statistically significant. The genotype and alleles distribution of rs4756195 and rs8193 showed no statistically significant difference (P>0.05). The haplotypes distribution of CAC, CGT, TAC, and TGT showed a significant difference between the 2 groups (P<0.05). The results of analysis of haplotypes and their interactions with relevant factors showed that breast cancer risk in the PR-negative group was significantly higher than that in the PR-positive group (P=0.016). We found an interaction between haplotypes and PR status.

Conclusions: The genotypes CT, CT+TT, TT, and allele T in rs13347 may be risk factors for breast cancer. The haplotype CAC may be a protective factor against breast cancer, and CGT, TAC, and TGT may be risk factors for breast cancer. The PR status interacts with CD44 gene SNP.

MeSH Keywords: Antigens, CD44 • Polymorphism, Single Nucleotide • Triple Negative Breast Neoplasms

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/907422

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Breast cancer is one of the most common tumors in women [1]. According to data released by the World Health Organization (WHO), the new cases of breast cancer reported in 2012 accounted for 25.2% of all female primary cancers. In China, the number of new cases of breast cancer was recently reported as 187 000, ranking first in the incidence rate of female cancers and posing a serious threat to the health and quality of life of Chinese women [2].

Cluster of Differentiation 44 (CD44) is a multi-structural and multi-functional transmembrane glycoprotein, which acts as the receptor of hyaluronic acids and many other extracellular matrix components, and is also the receptor of multiple growth factors and cytokines [3]. Most studies have shown that CD44 is involved in many key cellular processes, including cell growth, reproduction, differentiation, adhesion, and migration [4–8]. CD44 is also a common tumor marker closely related to the proliferation, migration, and invasion of tumor cells, as well as being involved in tumor-related angiogenesis. Studies have found that CD44 is widely expressed in a variety of cancer cells, affecting the prognosis of the disease, and that specific knockdown of CD44 inhibits the genesis and development of cancer [9].

There have been many studies on the single-nucleotide polymorphisms (SNPs) of breast cancer susceptibility genes. However, these SNP genes, including BRCA1 and BRCA2, can only explain about 25% of breast cancer susceptibility and morbidity. Previous studies have shown that the CD44 gene SNPs are detected in 84% of breast cancer patients and 68% of healthy people. Therefore, the CD44 gene may be one of the high-penetrance genes affecting breast cancer susceptibility [10]. There have been a few studies on the correlation of CD44 single-nucleotide polymorphism and the risk of breast cancer, which showed that CD44 gene SNPs can affect the susceptibility to breast cancer [11,12].

Therefore, in this study we selected 3 sites of CD44 single-nucleotide polymorphism: rs13347, rs4756195, and rs8193, and performed genotyping among the population in Beijing. Case-control studies were carried out to investigate the relationship between SNPs of CD44 gene and the susceptibility of breast cancer in the population of Beijing, China.

Material and Methods

Research objectives

For the case group, we randomly selected 225 breast cancer patients who were without family history and who were pathologically diagnosed in the Ruian People's Hospital of Zhejiang Province from January 2016 to December 2016. For the control group, we included 237 healthy women who came to the hospital for physical examination during the same period of time. The patients in the case group were 35–75 (53±7.93) years old, and the people in the control group were 34–78 (52.03±8.11) years old. The healthy people in the control group showed normal clinical and laboratory examination results and were without tumor history or family history. All the people in the case group and the control group signed informed consent and the study was approved by the Ethics Committee of Ruian People's Hospital of Zhejiang Province.

Sample collection

Subjects in the case group and the control group were instructed to fast for the morning before 2 ml of peripheral venous blood was collected. After ethylene diamine tetraacetic acid (EDTA) anticoagulation, the blood sample was sub-packed and stored in a freezer at –80°C.

Sample size estimation

According to the preliminary experiments and literature reports, the mutant allele frequency of CD44 in the control group (P_0) was set as 0.1, the odds ratio of the case group and the control group (OR) was set as 2, with α=0.05 and the power 1-β=0.85. The sample size was calculated by use of PASS 11.0, and the resulting sample size of each group was 196. There were more than 196 subjects in both groups, thus meeting the test requirements.

Polymorphic *loci* selection

We selected 3 SNPs on the CD44 gene based on 1 of the following screen conditions: I. It has been reported to be associated with breast cancer; II. It has heterozygosity and the minimum allele frequency (MAF) >0.05; III. It locates on the gene fragment that can cause functional changes. We selected the CD44 gene label tag SNPs in the Chinese population through the online site *http://gvs.gs.washington.edu/GVS144/* and searched for those with the minor allele frequency (MAF) >0.05 while r^2 >0.8. Finally, we found 3 representative SNP *loci* on the CD44 gene: rs13347, rs8193, and rs4756195. Detailed information on the selected SNP *loci* is shown in Table 1.

Genotyping

Polymerase chain reaction and ligase detection reaction (PCR-LDR) method was used to detect the polymorphism of the 3 SNP *loci* on CD44. PCR amplification products containing the target DNA were cut at the specific-recognition sites by restriction endonucleases, and the SNP *loci* were determined by gel

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Detailed information on the 3 SNP *loci* on CD44.

SNP	W>M*	Mutation position	MAF	Location
rs13347	C>T	3'UTR	0.29	11: 35231725
rs4756195	A>G	Intron	0.14	11: 35176485
Rs8193	C>T	3ÚTR	0.44	11: 35229771

* W means wild-type gene, M means mutant gene.

Table 2. The SNP primer sequences and product sizes.

SNP	Primer L	Primer R	Length
Rs13347	5'-AGGCTGAGACAGGAGGTTAT-3'	3'-CCAGAGTTACGCCCTTGAGA-5'	250 bp
Rs4756195	5'-TGCCTCCTGGTTCAAGTGAT-3'	3'-CGAGACCATCCTGGCTAACA-5'	314 bp
Rs8193	5'-TGGAAACATAACCATTACAGGGAG-3'	3'-CCAAGTGGGAACTGGAACGA-5'	220 bp

electrophoresis according to the size and number of restriction fragments. Primers were designed using data from the National Center for Biotechnology Information (NCBI) and the primer design software Primer Premier 5, and primers were synthesized by Invitrogen, Shanghai. The primer sequences are listed in Table 2.

Statistical analysis

IBM SPSS 21.0 software was used to analyze the results. The genotype and outcomes were tested by Hardy-Weinberg (H-W) equilibrium. The chi-square test was used to compare the genotype and allele frequencies as well as the degree of coincidence between the 2 groups. The odds ratio (OR) and the 95% confidence interval (CI) were calculated according to the characteristics of the data using the chi-square test and single-factor unconditional logistic regression analysis, and the results were used to compare the relative risks of breast cancer of the genotype with polymorphic *loci* mutations and that with wild-type homozygosity. Linkage disequilibrium analysis was conducted using SHEsis online software (*http://analysis.bio-x.cn/myAnalysis.php*). SNPStats online software (*http://bioinfo.iconcologia.net/snpstats/start.htm*) was used to construct haplotypes and analyze the interactions with related factors. The 2-sided hypothesis test was used and the significance level was set as α=0.05.

Results

Comparison of general data between groups

A total of 494 research subjects were enrolled in this study, including 242 patients with breast cancer and 252 healthy people as controls. The general data of the case group and the control group is shown in Table 3, and the group comparison results showed that there was no significant difference in age, body mass index (BMI), estrogen receptor (ER) status, progesterone receptor (PR) status, or human epidermal growth factor receptor-2 (HER-2) status between the 2 groups (P>0.05) (Table 3).

Hardy-Weinberg equilibrium analysis of the polymorphism genotypes in the 2 groups

The 3 SNPs of the CD44 gene were tested by Hardy-Weinberg equilibrium and the results were all in line with the equilibrium (P>0.05), suggesting that the subjects in this study had no significant natural selection or migration and that they were representative of the population (Table 4).

Distribution of the genotype and allele frequencies of the 3 SNP *loci* on CD44 gene in the case group and the control group

Single-factor logistic regression analysis showed that the distribution of the genotypes CC and CT, CC and DT+TT, and CC+CT and TT, as well as the frequency of C allele and T allele of locus rs13347, exhibited significant differences between the case group and the control group (P<0.05), suggesting that T allele might be a risk factor for breast cancer. There was no statistically significant difference between the distribution of genotypes and allele frequencies of loci rs4756195 and rs8193 between the 2 groups (P>0.05) (Table 5).

Correlation of CD44 haplotype with breast cancer risks

We analyzed the differences in haplotype distribution between the case group and the control group, and the results suggested that the haplotype CAC (OR=0.656, 95%CI:

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 3. The distribution of general physiological and biochemical indexes between the 2 groups.

Index	Grouping	Case group	Control group	t/χ^2	*P*
Ages		53.00±7.93	52.03±8.11	1.341	0.181
Age groups	≤50	93	111	1.607	0.205
	>50	149	141		
BMI	<25	143	165	2.144	0.143
	≥25	99	87		
Tumor grading	I	106			
	II	96			
	III	40			
Lymph node status	Positive	114			
	Negative	128			
Tumor size (cm)	T1: ≤2	96			
	T2: >2, ≤5	78			
	T3: >5	68		–	–
ER[a] status	Positive	123	114	1.545	0.214
	Negative	119	138		
PR[b]s status	Positive	139	135	0.747	0.387
	Negative	103	117		
Her-2[c] status	Positive	114	130	0.991	0.319
	Negative	128	122		

[a] ER – estrogen receptor; [b] PR – progesterone receptor; [c] Her-2 – human epidermal growth factor receptor 2.

Table 4. Hardy-Weinberg equilibrium analysis of the 3 SNP *loci* in the case group and the control group.

Grouping	SNP	WW	WM	MM	W	M	HWE χ^2	*P*
Case group	Rs13347	102	104	36	308	176	1.235	0.266
	Rs4756195	123	107	12	353	131	3.480	0.062
	Rs8193	116	97	29	329	155	1.524	0.217
Control group	Rs13347	138	94	20	370	134	0.498	0.480
	Rs4756195	140	102	10	382	122	2.678	0.102
	Rs8193	135	99	18	369	135	0.001	0.979

0.507~0.848, P=0.001) was a protective factor against breast cancer while the haplotypes CGT(OR=2.235, 95%CI: 1.161~4.304 P=0.014), TAC(OR=1.974, 95%CI: 1.347~2.893, P<0.001) and TGT(OR=2.313, 95%CI: 1.080~4.957 P=0.027) showed significantly higher distributions in the case group than in the control group, and therefore are risk factors for breast cancer (Table 6).

Interactive analysis of genotype and the related factors

We performed interactive analysis of CD44 haplotype and the related factors by analyzing the interactions of the 8 haplotypes of 3 SNPs *loci* with age, BMI, ER status, PR status, and HER-2 status, while the haplotype CAC served as the control. The results showed that there were interactions between haplotypes and PR (P =0. 016), but there was no interaction between haplotypes and age, BMI, ER, or HER-2 (P>0.05). Compared with the PR-positive haplotype CAC, the risk of breast cancer was increased by the haplotype CAC in the PR-negative group. The analysis results are shown in Table 7.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 5. Distribution of the genotype and allele frequencies of the SNP *loci* on CD44 gene in the case group and the control group.

SNP locus	Gene types	Case group	Control group	OR (95% CI)	*P*
Rs13347	CC	102 (42.1)	138 (54.8)	Reference	
	CT	104 (43.0)	94 (37.3)	2.435 (1.332–4.453)	0.004*
	TT	36 (14.9)	20 (7.9)	1.627 (0.881–3.005)	0.120
	CC	102 (42.1)	138 (54.8)	Reference	
	CT+TT	140 (57.9)	114 (45.2)	1.279 (1.075–1.521)	0.005*
	CC+CT	206 (85.1)	232 (92.1)	Reference	
	TT	36 (14.9)	20 (7.9)	1.874 (1.117–3.144)	0.015*
	C	308 (63.6)	370 (73.4)	Reference	
	T	176 (36.4)	134 (26.6)	1.368 (1.135–1.649)	0.001*
Rs4756195	AA	123 (50.8)	140 (55.6)	Reference	
	AG	107 (44.2)	102 (40.5)	1.366 (0.570–3.271)	0.484
	GG	12 (5.0)	10 (4.0)	1.144 (0.474–2.763)	0.765
	AA	123 (50.8)	140 (55.6)	Reference	
	AG+GG	119 (49.2)	112 (44.4)	1.106 (0.916–1.336)	0.292
	AA+AG	230 (95.0)	242 (96.0)	Reference	
	GG	12 (5.0)	10 (4.0)	1.250 (0.550–2.838)	0.594
	A	353 (72.9)	382 (75.8)	Reference	
	G	131 (27.1)	122 (24.2)	1.118 (0.904–1.384)	0.303
Rs8193	CC	116 (47.9)	135 (53.6)	Reference	
	CT	97 (40.1)	99 (39.3)	1.875 (0.90–3.550)	0.054
	TT	29 (12.0)	18 (7.1)	1.644 (0.857–3.154)	0.135
	CC	116 (47.9)	135 (53.6)	Reference	
	CT+TT	126 (52.1)	117 (46.4)	1.121 (0.937–1.342)	0.210
	CC+CT	213 (88.0)	234 (92.9)	Reference	
	TT	29 (12.0)	18 (7.1)	1.678 (0.957–2.940)	0.067
	C	329 (68.0)	369 (73.2)	Reference	
	T	155 (32.0)	135 (26.8)	1.196 (0.985–1.452)	0.071

Discussion

The human CD44 gene is located on the short arm of chromosome 11, and consists of 20 highly conserved exons. Hyaluronic acid (HA) is an important component of the extracellular matrix in mammalian tissues, and all CD44 isoforms contain HA structures in the extracellular domain. The combination of HA and CD44 not only affects cell adhesion, but also stimulates specific functions of various tumor cells to promote breast cancer progression [13].

The results of this study showed that there were no significant differences in the distribution of alleles at the rs13347 locus on the CD44 gene between the case group and the control group. Compared with the CC genotype, the TT and CT+TT genotypes appeared to increase the risk of breast cancer. Previous studies on single-nucleotide polymorphisms in the CD44 gene have found that SNPs at the rs13347 locus can significantly increase the risk of breast cancer in the Chinese Han population [14–16], which is consistent with our results in the present study. However, other studies showed that rs13347

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 6. Relationship between haplotype of CD44 gene and breast cancer risks.

Haplotype*	Case group (n=484)		Control group (n=504)		χ^2	OR (95% CI)		P
CAC[a]	166.15	(0.343)	223.52	(0.443)	10.379	0.656	[0.507~0.848]	0.001
CAT	66.90	(0.138)	75.06	(0.149)	0.230	0.917	[0.642~1.309]	0.632
CGC	46.34	(0.096)	57.64	(0.114)	0.910	0.820	[0.545~1.234]	0.340
CGT[a]	28.61	(0.059)	13.78	(0.027)	6.070	2.235	[1.161~4.304]	0.014
TAC[a]	82.00	(0.169)	47.21	(0.094)	12.463	1.974	[1.347~2.893]	<0.001
TAT	37.95	(0.078)	36.21	(0.072)	0.153	1.099	[0.685~1.765]	0.696
TGC	34.52	(0.071)	40.63	(0.081)	0.305	0.876	[0.546~1.404]	0.581
TGT[a]	21.54	(0.045)	9.95	(0.020)	4.909	2.313	[1.080~4.957]	0.027

OR – odds ratio; CI – confidence interval. * Haplotypes were sorted according to the order of rs13347, rs4756195, and rs8193.
[a] The haplotype was significantly correlated with breast cancer risks ($p<0.05$).

Table 7. Interactive analysis of CD44 SNP haplotype and PR status.

Haplotype	frequency	OR (95% CI)	
		PR+ group	PR– group
CAC	0.3932	1.00	2.63 (1.08–6.44)
CAT	0.1447	1.09 (0.58–2.05)	1.93 (0.80–4.68)
TAC	0.1292	0.77 (0.36–1.66)	0.44 (0.18–1.07)
CGC	0.1073	0.86 (0.37–2.00)	1.96 (0.82–4.70)
TGC	0.0767	1.49 (0.57–3.94)	1.67 (0.55–5.04)
TAT	0.0767	0.46 (0.19–1.09)	2.77 (0.73–10.47)
CGT	0.0410	0.45 (0.11–1.93)	0.41 (0.04–4.47)
TGT	0.0311	0.88 (0.16–4.69)	——

single-nucleotide polymorphisms were not significantly correlated with risk of breast cancer in the northern population of India [12], which may be explained by the different susceptibility to breast cancer of people from different countries with different genetic backgrounds.

In addition, our results showed that the distribution of alleles at locus rs4756195 and locus rs8193 exhibited no statistically significant difference between the case group and the control group. Analysis of SNPs of locus rs4756195 has not been reported abroad, but it has been reported in China [17] that the polymorphisms of locus rs4756195 on CD44 are associated with breast cancer risks among women of Han ethnicity in Chongqing, China, and that the AG and GG genotypes are susceptible genotypes of breast cancer in these women, while the GG genotype may be associated with poor prognosis of breast cancer. In the present study, we did not find an impact of rs4756195 on breast cancer susceptibility, which may be due to polygenic influences and multiple environmental factors. The expression of traits is influenced not only by genotypes, but also by lifestyle, nutritional status, geographical environment, economic level, and difference in sample quantities, as well as the introduction of possible confounding factors and sampling errors, all of which potentially affect the results. There have been few studies on this locus, so further research is needed to verify our results. We also found that locus rs8193 was not associated with breast cancer susceptibility. There have been relatively few studies on locus rs8193, and to date there is no report on the relationship between rs8193 single-nucleotide polymorphisms and breast cancer risks. However, a study found that the rs8193 allele T can increase the incidence of skin adverse reactions after radiotherapy in breast cancer patients [18], while another group found that the SNP at locus rs8193 is a risk factor for colon cancer prognosis [19].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

The genesis and development of diseases is usually not the result of a single allele, but instead is the consequence of interactions of multiple SNP loci, which could be passed on to offspring in the form of haplotypes. The phenotype is also influenced by other non-genetic factors. Therefore, constructing haplotypes and analyzing their interactions with non-genetic factors might contribute to the study of disease pathogeneses [20]. By analyzing distribution differences of haplotypes in the case group and the control group, we found that the haplotype CAC is a protective factor against breast cancer (OR=0.656, 95%CI: 0.507~0.848, P=0.001), while the haplotypes CGT, TAC, and TGT are risk factors for breast cancer (the distributions of these 3 haplotypes were significantly higher in the case group than in the control group). In addition, through interactive analysis of haplotypes and other factors, we found that there were interactions between haplotype CAC of the 3 *loci* on CD44 and PR (P =0. 016), and that the breast cancer risk of the PR-negative group with haplotype CAC was 2.63 times higher than in the PR-positive group (OR=2.63, 5%CI: 1.08–6.44). There were no interactions between haplotypes and other factors such as age, BMI, ER, or HER-2 (P>0.05). The mammary gland is one of the main target organs of sex hormones. Both endogenous and exogenous estrogen and progesterone can affect mammary gland and may participate in the pathogenesis and development of breast cancer [21]. Breast cancer is a hormone-dependent tumor. ER/PR-negative breast cancers lack the target for endocrine therapy and therefore are associated with worse prognoses than are ER/PR-positive breast cancers. In this study, we found that CD44 SNPs have potential interactions with PR status, which influences breast cancer susceptibility. Further research is needed to validate these results.

Conclusions

By comparing the distribution patterns of each haplotype in the case group and the control group, we found a haplotype that might reduce the risk of breast cancer. The interactive analysis of haplotypes and age, BMI, or other related factors contributed to the further discovery of the combined effects of genetic factors and non-genetic factors on breast cancer susceptibility. In addition, since there are few studies on the relationship between the 3 SNP *loci* on the CD44 gene and breast cancer risks, this study may provide a theoretical basis for clinical and scientific research, but further studies are needed to validate our findings.

Conflict of interest

None.

References:

1. Xu J: Cancer Statistics, 2010. Cancer J Clin, 2011; 61: 10–29
2. Fitzmaurice C, Allen C, Barber RM et al: Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. JAMA Oncol, 2017; 3: 524–28
3. Zöller M: CD44, hyaluronan, the hematopoietic stem cell, and leukemia-initiating cells. Front Immunol, 2015; 6: 235
4. Mckallip RJ, Fisher M, Gunthert U et al: Role of CD44 and its v7 isoform in staphylococcal enterotoxin B-induced toxic shock: CD44 deficiency on hepatic mononuclear cells leads to reduced activation-induced apoptosis that results in increased liver damage. Infect Immun, 2005; 73: 50–61
5. Wu X, He X, Shi L et al: Long non-coding RNA ucoo2kmd.1 Regulates CD44-dependent cell growth by competing for miR-211-3p in colorectal cancer. PLoS One, 2016; 11: e0151287
6. Zohar R, Suzuki N, Suzuki K et al: Intracellular osteopontin is an integral component of the CD44-ERM complex involved in cell migration. J Cell Physiol, 2000; 184: 118–30
7. Alam TN, O'Hare MJ, Laczkó I et al: Differential expression of CD44 during human prostate epithelial cell differentiation. J Histochem Cytochem, 2004; 52: 1083–90
8. Smith SM, Li C: Cell specific CD44 expression in breast cancer requires the interaction of AP-1 and NFκB with a novel cis-element. PLoS One, 2012; 7: e50867
9. Misra S, Ghatak S, Patil N et al: Novel dual cyclooxygenase and lipoxygenase inhibitors targeting hyaluronan-CD44v6 pathway and inducing cytotoxicity in colon cancer cells. Bioorg Med Chem, 2013; 21: 2551–59
10. Zhou J, Nagarkatti PS, Zhong Y et al: Unique SNP in CD44 intron 1 and its role in breast cancer development. Anticancer Res, 2010; 30: 1263–72
11. Zhou J, Nagarkatti PS, Zhong Y et al: Implications of single nucleotide polymorphisms in CD44 Exon2 in risk for breast cancer. Eur J Cancer Prev, 2011; 20: 396–402
12. Tulsyan S, Agarwal G, Lal P et al: CD44 gene polymorphisms in breast cancer risk and prognosis: A study in North Indian population. PLoS One, 2013; 8: e71073
13. Bourguignon LY, Wong G, Earle C et al: Hyaluronan-CD44 interaction promotes c-Src-mediated twist signaling, microRNA-10b expression, and RhoA/RhoC up-regulation, leading to Rho-kinase-associated cytoskeleton activation and breast tumor cell invasion. J Biol Chem, 2010; 285: 36721–35
14. Jiang L, Deng J, Zhu X et al: CD44 rs13347 C>T polymorphism predicts breast cancer risk and prognosis in Chinese populations. Breast Cancer Res, 2012; 14: R105
15. Wu H, Deng J, Zheng J et al: Functional polymorphisms in the CD44 gene and acute myeloid leukemia cancer risk in a Chinese population. Mol Carcinog, 2015; 54: 102–10
16. Wu XM, Yang HG, Zheng BA et al: Functional genetic variations at the microRNA binding-site in the CD44 gene are associated with risk of colorectal cancer in Chinese populations. PLoS One, 2015; 10: e0127557
17. Zhou Xin WC: [Association of CD44 polymorphisms with genetic susceptibilities and clinico-pathologic characteristics in breast cancer.] Sichuan Da Xue Xue Bao Yi Xue Ban, 2012; 43(6): 807–11 [in Chinese]
18. Suga T: Haplotype-based analysis of genes associated with risk of adverse skin reactions after radiotherapy in breast cancer patients. Int J Radiat Oncol Biol Phys, 2007; 69(3): 685–93
19. Gerger A, Zhang W, Yang D et al: Common cancer stem cell gene variants predict colon cancer recurrence. Clin Cancer Res, 2011; 17: 6934–43
20. Moore JH: The ubiquitous nature of epistasis in determining susceptibility to common human diseases. Hum Hered, 2003; 56: 73–82
21. Rossouw JE, Anderson GL, Prentice RL et al: Risks and benefits of estrogen plus progestin in health postmenopausal women: Principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA, 288: 321–33

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]