A single nucleotide polymorphism in codon F31I and V57I of the AURKA gene in invasive ductal breast carcinoma in Middle East

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Abstract
Although few studies have suggested a carcinogenic role for polymorphism of F31I and V57I codons of AURKA gene in invasive ductal carcinoma, contradictory results from different populations mandates regional investigations. We aimed to determine polymorphisms of F31I and V57I codons of AURKA gene and their association with cancer prognosis in patients compared with controls in an eastern population of Iran.

A case-control study was conducted on specimens from 100 patients and 100 age- and gender-matched controls. DNA was extracted and the codons F31I and V57I were amplified. The different genotypes were analyzed by PCR-RFLP and electrophoresis.

In codon F31I, the frequency of Phe/Ile was 70% and 82% in patients and healthy controls respectively, whereas (Ile/Ile) was 30% in patients and 18% in healthy (\(P = .047\)). Analyzing V57I genotypes showed a higher homozygote Val/Val genotype in patients compared with controls (76% vs 68%), whereas the frequency of heterozygous Val/Ile genotype was lower in patients (17%) than controls (30%), yielding a marginal association between breast cancer and Val/Val genotype (\(P = .048\)). No association was observed between SNPs of either F31I or V57I genotypes and histological grades. However, there was a significant association between tumor stages and F31I genotype (\(P\) for trend = .003).

This is the first report of F31I and V57I polymorphisms in AURKA gene in breast cancer in Iran. Determination of allelic polymorphism of those codons will help to understand background genetic predisposition and could have prognostic value in management of breast cancer in the target population.

Abbreviations: PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism analysis.

Keywords: AURKA gene, breast cancer, F31I codon V57I codon, invasive ductal carcinoma

1. Introduction
Breast cancer is common, with about 1.7 million new cases and more than 0.5 million deaths in 2012\textsuperscript{[1]}; its incidence is increasing.\textsuperscript{[2]} The average age at diagnosis is relatively low in some regions in Iran\textsuperscript{[3]}. Resistance to chemotherapy in breast cancer may be due to genetic and epigenetic changes in metastatic breast cancer.\textsuperscript{[4]}

The aurora kinases regulate important events in the cell cycle. Aurora A kinase is encoded by the gene AURKA, also known as STK15 (serine/threonine kinase 15).\textsuperscript{[5]} It regulates the G2 to M transition into mitosis. Nonsynonymous AURKA polymorphisms (91T/A and 169G/A) encode phenylalanine/isoleucine (F31I) and valine/isoleucine (V57I). These polymorphisms have been linked with cancers, including breast cancer, identifying AURKA as a possible oncogene/cancer susceptibility gene. AURKA is located on chromosome 20 (20q13.2). Its product is a protein of 403 amino acids with regulatory and catalytic domains.\textsuperscript{[6,7]} The catalytic domain has a serine/threonine kinase activity role. AURKA may be amplified and is overexpressed in many malignancies including invasive carcinomas of ovary, head and neck, and breast.\textsuperscript{[8–10]} Overexpression mechanisms and effects of AURKA in carcinomas are not yet fully understood. Aurora kinase A controls cell cycle checkpoints and has roles in centrosome division, cytokinesis, and cytokinesis. Overexpression may cause genomic instability via dysregulation of the cell cycle, leading to tumor development.\textsuperscript{[11,12]} AURKA has been investigated as a drug target in many animal-model trials.\textsuperscript{[13,14]}

Many studies have suggested that both polymorphisms (F31I and V57I) are associated with risk of breast cancer.\textsuperscript{[15–18]} Cox et al found an association between breast carcinoma and F31I and V57I homozygote alleles in postmenopausal women in the USA.\textsuperscript{[16]} Similar findings have been discussed by Ewart-Toland et al who identified AURKA as a low-penetrance tumor-susceptibility gene in mice and humans.\textsuperscript{[17]} Sun et al found that aurora A kinase Ile/Ile 31 homozygosity was associated with
increased risk of breast carcinoma in an Asian population. A meta-analysis by Dai et al found the isoleucine-encoding AURKA polymorphism rs2273535T/A (Phe31Ile) increased the risk of breast cancer in Asians but not Caucasian while the isoleucine-encoding rs1047972G/A Val57Ile polymorphism reduced breast cancer risk in Caucasians but not Asians. There remains a need for further data on the contribution of AURKA single nucleotide polymorphisms to breast cancer risk in different human populations, some of which are very poorly represented in the published literature.

Furthermore, few studies anywhere have examined the possible interactions of the SNPs responsible for the F31I and V57I aurora kinase polymorphisms with important pathological determinants of breast cancer behavior in different populations. This study is the first attempt to investigate the polymorphisms in SNP of F31I and V57I codons of AURKA gene in breast cancer in Iranian patients, including their prognostic value.

2. Methods and materials
In this case-control study, 100 women with breast cancer and 100 healthy controls were compared. The 2 groups were age-matched with comparable age (mean 47.3 ± 12.8 and 48.1 ± 12.5 years, respectively).

2.1. Histopathological studies
Representative tissue samples were collected from 100 women diagnosed with invasive ductal carcinoma between 2011 and 2015 in the main hospitals of Sabzevar district, North-East Iran. Samples including tumor tissue were taken for diagnosis and treatment.

The typical surgical specimens were ranged 10 to 25 mm in size. All parts of tumor were cut and blocked sequentially every 2 mm in paraffin wax according to our standard practice protocol of histopathology irrespective of the tumor size. Each block was then sectioned into 3-μm thick tissues to mount on slides. The 3-μm sections stained with hematoxylin and eosin were examined by 2 expert pathologists. The pathologists classified each carcinoma using standard criteria for stage and grade. Grade (from 1 to 3) was based on mitosis counts, nuclear pleomorphism, and acinar differentiation. The presence or absence of necrosis, maximum size of the lesion, and surgical margins were also recorded. Staging employs the standard TNM system.

2.2. DNA extraction
DNA was extracted using a standard kit (QIAGEN, Manchester, UK). Peripheral blood samples were collected from all healthy controls in 1.5 mL tubes containing 0.5 mM EDTA and stored at −20°C or −70°C until required. Stored blood was thawed and diluted with PBS and cells were separated by Ficoll-Hypaque gradient centrifugation. Prepared blood samples from healthy control were used for polymerase chain reaction restriction fragment length polymorphism analysis (PCR-RFLP). For patients, 5-μm tumor sections were deparaffinized for DNA extraction. We used spectrophotometer UV and gel electrophoresis to assess DNA quality.

2.3. Polymerase chain reaction restriction fragment length polymorphism analysis
Codons F31I and V57I of AURKA exon 4 were amplified, using lyophilized primers diluted to 5 mM dNTP (stoke 10 mM) with deionized sterile water, according to manufacturer’s instructions (Genet Bio, South Korea). The primer sequences were as follows:
Forward: CTTTCATGAATGCGAAGAGTT and Reverse: TCTGCTTCTTCTGATTCTGAAAGC.

Annealing at 53°C for 60 seconds for 38 amplification cycles gave optimal amplification (Astech, Japan). Each tube for polymerase chain reaction (PCR) composed of 2.5 μL 10 × buffer, 0.8 μL of each primer, 5 μL of DNA, 0.5 μL of dNTP, 2.5 μL of magnesium chloride, and DNA polymerase enzyme at 0.2 μL which were diluted to the final volume of 25 μL using distilled water.

A standard electrophoresis protocol was performed using 1.5% agarose gel, 5 μL of each PCR product and 1 μL of loading dye for each, well stained with ethidium bromide (EtBr). Electrophoresis photographs were taken by gel documentation machine (Bio-Rad, Hercules, CA).

2.4. Restriction fragment length polymorphism analysis
For determination of genotype (polymorphism) of PCR products, restriction fragment length polymorphism analysis (RFLP) was performed using 2 different enzymes, Apol and BstUI. With either XapI (Apol) or BstUI at 2 μL, a solution composed of Tango 10x buffer 2 μL, nuclease-free water 18 μL, and PCR reaction mixture 10 μL (Thermo Scientific, Lithuania) was used. All samples were incubated at 37°C for 2 hours. They were then run on 2.5% agarose gel and photographs taken after completion.

2.5. Statistical analyses
To compare the proportion of cases and controls with a specific polymorphism, Chi square and Fisher exact tests were used. The trend of associations between cancer stages and either F31I or V57I polymorphisms were tested using cross-tabulations and P for trend test. For analysis of survival rate, survival distribution and their associations Kaplan-Meier and log-rank tests were performed. Differences between cases and controls were taken as significant if P < 0.05 (2-sided probability). To have an estimate of sample size in original plan, assuming presence of Phele genotype of codon F31I in 85% of controls and 65% of cancer population, 0.05 type I error and 0.80 type II error, minimum sample size were 82. Data was analyzed using IBM SPSS package version 22 (IBM UK, Hampshire, England).

2.6. Ethical considerations
The protocol of the study has been reviewed by medical ethics committee of Sabzevar University of Medical Science and has been approved under Medsab.IR.REC.1393.16. This study used project-specific resources and investigators have rights to share relevant data after examining the potential collaboration projects by the relevant research committee.

3. Results
3.1. Demographic data
The present study was conducted on 200 women: 100 with in situ or invasive ductal breast carcinoma (mean ±SD age 47.25 ± 12.80 years). The healthy control group were age-matched women (mean ±SD age of 48.08 ± 12.50 years). The age range was 25 to 86 years for patients and 23 to 80 years for healthy controls.
3.2. **Histopathological findings**

3.2.1. **Grade.** There were 19 (19%) grade 1 carcinomas, 51 (51%) grade 2, and the remaining 30 (30%) were grade 3 (Fig. 1).

3.2.2. **Stage.** There were 37 cases in disease stage of 0 (carcinoma in situ) or I, of which 11 samples had in situ carcinoma only, whereas 26 were stage I invasive carcinomas without lymph nodes involvement.

In 39 cases, lymph nodes or adjacent tissues were involved (stage II). In 13 cases, the cancer spread to internal mammary lymph nodes; in some cases even the chest wall was invaded (stage III). In the remaining cases of invasive ductal carcinoma, 11 cases were at stage IV (metastatic).

3.3. **Genotype polymorphism frequencies**

3.3.1. **Polymorphism of codon F31I.** Table 1 shows the frequencies for heterozygote phenylalanine/isoleucine (Phe/Ile) and homozygote isoleucine/isoleucine (Ile/Ile). The frequency of Phe/Ile was 70 (70%) and 82 (82%) in patients and healthy controls, respectively, whereas (Ile/Ile) was 30 (30%) in patients and 18 (18%) in healthy controls. This indicates an association between cancer risk and high Ile/Ile/ low Phe/Ile frequencies compared with control ($P = .047$). There was no phenylalanine/phenylalanine (Phe/Phe) genotype. Figure 2 shows examples of ethidium bromide-stained gels illustrating PCR-RFLP assessment with restriction enzyme Apol of the F31I codon with examples of heterozygote Phe/Ile and homozygote Ile/Ile.

3.3.2. **Polymorphism of V57I.** There was a higher homozygote valine/valine (Val/Val) in patients compared with controls (76% vs 68%), whereas the frequency of heterozygous Val/Ile genotype was lower in patients (17%) than controls (30%), yielding a marginal association between breast cancer and high Val/Val and low Val/Ile genotype, compared to controls ($P = .048$). Higher cancer risk in terms of OR (95% CI) was 1.9723.

| Table 1                      | The frequency of genotype polymorphism of codons F31I and V57I of AURKA gene in case and control samples. |
|-----------------------------|---------------------------------------------------------------------------------------------------------|
| Polymorphism                | Cancer n, %                                                                                          | Control n, % | Total             |
| Codon F31I genotype         |                                                                                                       |              |                   |
| Phe/Ile (phenylalanine/isoleucine) | 70 (70%)                                                                                   | 82 (82%)     | 152               |
| Ile/Ile (isoleucine/isoleucine)   | 30 (30%)                                                                                   | 18 (18%)     | 48                |
| Phe/Phe (phenylalanine/phenylalanine) | 0                                                                                              | 0             | 0                 |
| Codon V57I genotype         |                                                                                                       |              |                   |
| Val/Val (valine/valine)      | 76 (76%)                                                                                   | 68 (68%)     | 144               |
| Val/Ile (valine/isoleucine)  | 17 (17%)                                                                                   | 30 (30%)     | 47                |
| Ile/Ile (isoleucine/isoleucine) | 7 (7%)                                                                                       | 2 (2%)       | 9                 |
(1.0002–3.8893) for high Val/Val and low Val/Ile in cancer group compared with controls.

The homozygous Ile/Ile genotype was found in 7 (7%) and 2 (2%) of patients and healthy controls, respectively (Table 1). Association of this genotype with cancer could not be tested because of small numbers.

Figure 3 shows BstUI digestion products for the V57I codon. Restriction fragments for heterozygote Val/Ile and homozygote Val/Val are shown. Figure 4 demonstrates BstUI restriction fragments of the PCR products for V57I codon showing heterozygote Val/Ile and noncut homozygote Ile/Ile genotypes.

3.4. Association of tumor grade and stage with polymorphisms of F31I and V57I

No significant associations existed between the F31I or V57I genotypes and carcinoma grade (Table 2). There was however a statistically significant association between F31I polymorphism and stage of cancer, indicating lower frequency of Phe/Ile genotype and higher frequency of Ile/Ile at the more advanced tumor stage \( (P = .019, P \text{ for trend} = .003) \). No significant association between V57I genotype and stage was observed.

3.5. Follow up and surviving rate

All cases with invasive ductal carcinoma were followed up for a minimum of 30 months (Fig. 5). There was no significant association between survival and any specific genotype in codon V57I. However, mean survival was worse for patients who were homozygote for Ile/Ile in codon F31I compared with other genotypes \([20.9 (95\% \text{ CI: 14.1–27.7})]\).

4. Discussion

Genetic and epigenetic factors influencing breast cancer risk include polymorphisms involving genes, including AURKA. Allele frequencies vary in different human populations. Despite wide investigation, the contribution of AURKA V57I and F31I polymorphisms to breast cancer risk is still controversial:

![Figure 2](image2.png)

**Figure 2.** PCR-RFLP products lines for F31I codon after adding ApoI enzyme. The PCR product total length was 230 bp total length. The length of the cut sections were 75 and 155 bp. Ladder was 50 bp for PCR-RFLP. PCR = polymerase chain reaction, PCR-RLFP = polymerase chain reaction restriction fragment analysis.

![Figure 3](image3.png)

**Figure 3.** PCR-RFLP products lines for V57I codon after adding BstUI enzyme. Note the restriction fragments for heterozygote Val/Ile and homozygote Val/Val. Bands 1 to 7 are PCR products of cancer specimens. PCR = polymerase chain reaction, PCR-RLFP = polymerase chain reaction restriction fragment length polymorphism analysis.

![Figure 4](image4.png)

**Figure 4.** PCR-RFLP products lines for V57I codon after adding BstUI enzyme. Note the length of cuts after digestion for heterozygote Val/Ile, and noncut homozygote Ile/Ile. The PCR product total length was 230 bp. The length of the cut sections were 65 and 165 bp. PCR = polymerase chain reaction, PCR-RLFP = polymerase chain reaction restriction fragment length polymorphism analysis.
conflicting results mean any definite association between either AURKA V57I or F31I and breast cancer remains elusive.

AURKA helps to maintain chromosome integrity after DNA damage.[20] A role for nonsynonymous AURKA polymorphisms in carcinogenesis is at least mechanistically plausible.[21,22] Nikonova et al showed association of overexpression of AURKA with defective mitotic spindles, supernumerary centrosomes, chromosomal instability, aneuploidy, and apoptosis resistance.[5] In Finland, Staff et al reported AURKA overexpression in 21% of 126 patients with breast cancer.[15] Overexpression of AURKA is associated with autophagy inhibition[23] and Taxol resistance in breast cancer.[24] Studies in Chinese Han population showed associations between AURKA polymorphisms and breast cancer risk; the association was stronger when another polymorphism in BRCA1 was present.[22]

A meta-analysis of 14 case-control studies of cancer susceptibility comprising 11,245 cases, and 16,024 controls suggested a protective effect of AURKA V57I polymorphism, especially in Caucasians, rather than Asians; analysis by ethnicity indicated a decreased risk of breast cancer in Caucasians specifically. However, even the large sample size did not provide enough statistical power for definitive conclusions.[21]

King et al claimed a role in mammary carcinogenesis for the F31I polymorphism, but not for V57I.[25] Qin et al showed that the F31I Ile/Ile allele predisposes Asians and Caucasians women to breast cancer, but found no significant association between the V57I polymorphism and breast cancer risk.[27] In contrast, Fletcher et al found no consistent association between breast cancer risk and the F31I polymorphism in white women of British descent. However, their results may reflect the potential geographic-dependent genetics risk factors in the UK. Additionally, statistically significant heterogeneity in odds ratio estimates may reflect population-specific linkage disequilibrium with a functional variant or artifacts, including population stratification or publication bias.[28]

These conflicting findings suggest that other factors may modify associations between F31I and V57I AURKA polymorphisms and breast cancer, which could be regional dependent. In interpretation of results, we should acknowledge that these studies in different regions had different sample size and method of analysis, and did not include all life-style and environmental factors, including diet, physical activities, and various exposure to hormone replacement therapy. If there is any consensus, it is that the F31I polymorphism does modify breast cancer risk. Tang

| Characteristics | F31I | V57I |
|-----------------|------|------|
| Phe/Ile n, %    | Ile/Ile n, % | Val/Val n, % | Val/Ile n, % | Ile/Ile n, % |
| Stage of cancer |      |      |      |      |      |
| 0/I             | 30 (43%) | 7 (23%) | 29 (38%) | 6 (35%) | 2 (29%) |
| II              | 28 (40%) | 11 (37%) | 30 (39%) | 7 (41%) | 2 (29%) |
| III             | 9 (13%)  | 4 (13%)  | 10 (13%) | 2 (12%) | 1 (14%) |
| IV              | 3 (4%)   | 8 (27%)  | 7 (9%)   | 2 (12%) | 2 (29%) |
| Statistical significance | X^2P value = .019; P for trend = .003 | NS |

| Grade of tumor | F31I | V57I |
|----------------|------|------|
| 1              | 12 (17%) | 7 (23%) | 16 (21%) | 3 (18%) | 0 (0%) |
| 2              | 40 (57%) | 11 (37%) | 42 (55%) | 7 (41%) | 2 (29%) |
| 3              | 18 (26%) | 12 (40%) | 18 (24%) | 7 (41%) | 5 (71%) |
| Statistical significance | NS | NS |

Figure 5. Association between patients’ survival and single nucleotide in codon V57I (left) or codon F31I (right). Note only patients with Ile/Ile genotype in codon V57I had significantly worst survival rate.
et al in their meta-analysis study of 19,267 cancer cases and 24,359 controls supported this conclusion concerning the F311 polymorphism and breast cancer.[28]

The main goal of our study was to examine association (if any) between the cancer risk and polymorphisms of AURKA F311 and V57I codons in the North-East Iran. Our results were in agreement with most of aforementioned studies and showed a higher frequency for homozygous Ile/Ile genotypes at the F311 locus in patients with breast cancer compared to healthy controls in North-East Iran. To the best of our knowledge, it is the first report to find an association between F311 Ile/Ile homozygosity and breast cancer in the Middle East. It is possible that the higher incidence of invasive ductal carcinoma in this area could be linked to a higher frequency of the Ile coding allele at F311 genotype. We also observed a significant association between the Ile/Ile F311 genotype and higher stage of breast carcinoma in our patients. Ruan et al reported an association between homozygote (Ile/Ile) genotype of F311 codon (rs2273335) and significant increased risk of breast cancer among the Chinese Han population.[12,21] Dai et al showed elevated risk of breast cancer in association with Phen/le and Ile/Ile genotypes at codon 31 of the AURKA gene.[10,23] They also found an association between breast cancer risk, obesity, and Ile/Ile homozygosity. In another study in which Caucasians were recruited Dai and colleagues reported the same result between breast cancer and homozygote Ile/Ile genotypes at F311 codon.[22]

To explore the mechanism of the AURKA gene mutations in the development and progression of the breast cancer, a new study suggested that AURKA protein kinase is involved in vasculogenic mimicry of cancer stem cells and may become a new treatment target in suppressing vasculogenic mimicry and metastasis of breast cancer.[31]

Our study also showed that patients with the shortest survival had more homozygote Ile/Ile in codon F311 and had higher tumor stages compared with other cases, supporting an association between breast cancer and homozygote Ile/Ile genotypes at AURKA codon 31.[11] Of course, many other factors influence breast carcinogenesis, including hormone receptors and TP53 with its important role in apoptosis.

Further studies with larger sample size and longer follow-up can be justified to let us address outstanding controversies in this area. Breast cancer risk stratification is important for earlier detection and more effective treatment. Economic and cultural obstacles to effective breast cancer management also need to be addressed.

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**References**

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available at: http://globocan.iarc.fr. Accessed on September 10, 2015.

2. Youden DR, Cramb SM, Yip CH, et al. Incidence and mortality of female breast cancer in the Asia-Pacific region. Cancer Biol Med 2014;11:101–15.

3. Golmohammadi R, Pehjan A. The prognostic value of the P53 protein and the Ki67 marker in breast cancer patients. J Pak Med Assoc 2012;62:871–5.

4. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. J Pathol 2005;205:275–92.

5. Nikonova AS, Astarakov I, Serebriiskii IG, et al. Aurora A kinase (AURKA) in normal and pathological cell division. Cell Mol Life Sci 2013;70:661–87.

6. U.S. National Library of Medicine. AURKA aurora kinase A [Homo sapiens (human)] Gene ID: 6790. National Center for Biotechnology Information. Available at: NCBI.nlm.nih.gov/gene/6790. Accessed on September 13, 2015.

7. Abba MC, Lucanu E, Butti M, et al. Breast cancer biomarker discovery in the functional Genomic Age: a systematic review of 42 gene expression signatures. Biomark Insights 2010;5:103–18.

8. Kollareddy M, Dzubak P, Zheleva D, et al. Aurora kinases: structure, functions and their association with cancer. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2008;152:27–33.

9. Liu C. The association between AURKA T91A polymorphism and breast cancer risk. Breast Cancer Res Treat 2011;129:281–9.

10. Chou CH, Yang NK, Liu TY, et al. Chromosome instability modulated by BM11-AURKA signaling drives progression in head and neck cancer. Cancer Res 2013;73:953–66.

11. Jiang S, Katayama H, Wang J, et al. Estrogen-induced aurora kinase-A (AURKA) gene expression is activated by GATA-3 in estrogen receptor-positive breast cancer cells. Horm Cancer 2010;1:11–20.

12. Eterno V, Zambelli A, Villani L, et al. Aurora kinase inhibitors: rising stars in cancer therapeutics? Mol Cancer Ther 2010;9:268–78.

13. Gautschi O, Heghvay J, Mack PC, et al. Aurora kinases as anticancer drug targets. Clin Cancer Res 2008;14:1639–48.

14. Staff S, Isola J, Jumpannen M, et al. Aurora-A gene is frequently amplified in basal-like breast cancer. Oncol Rep 2010;23:307–12.

15. Cox DG, Hankinson SE, Hunter DJ. Polymorphisms of the AURKA (STK15/Aurora kinase) gene and breast cancer risk (United States). Cancer Causes Control 2006;17:81–3.

16. Ewart-Toland A, Briassoulis P, de Konig JP, et al. Identification of S66/S6STK15 as a candidate low-penetrance tumor-susceptibility gene in mouse and human. Nat Genet 2003;34:403–12.

17. Sun T, Xiao X, Wang J, et al. Functional Phen31Ile polymorphism in Aurora A and risk of breast cancer. Carcinogenesis 2004;25:2225–30.

18. Dai ZJ, Kang HF, Wang XJ, et al. Association between genetic polymorphisms in AURKA (rs2273335 and rs1047972) and breast cancer risk: a meta-analysis involving 37,221 subjects. Cancer Cell Int 2014;14:91.

19. Pan JT, Ajani JA, Gu J, et al. Association of Aurora-A (STK15) kinase polymorphisms with clinical outcomes of esophageal cancer treated with neoadjuvant chemoradiation. Cancer 2012;118:5456–53.

20. Tatsuka M, Sato S, Kitajima S, et al. Overexpression of Aurora-A potentiates HRAS-mediated oncogenic transformation and is implicated in oral carcinogenesis. Oncogene 2005;24:1122–7.

21. Ruan Y, Song AP, Wang H, et al. Genetic polymorphisms in AURKA and BRCA1 are associated with breast cancer susceptibility in a Chinese Han population. J Pathol 2011;225:535–43.

22. Zhou Z, Yuan Z, Zhang Q, et al. Aurora kinase A inhibition-induced autophagy triggers drug resistance in breast cancer cells. Autophagy 2012;8:1798–810.

23. Li Y, Tang K, Zhang H, et al. Function of Aurora kinase A in taxol-resistant breast cancer and its correlation with Pgp. Mol Med Rep 2011;4:4719–46.

24. Tang W, Qiu H, Jiang H, et al. Aurora-A V57I (rs1047972) polymorphism and cancer susceptibility: a meta-analysis involving 27,269 subjects. PLoS One 2014;9:e90328.

25. King MC, Marks JH, Mandell JB. New York Breast Cancer Study GroupBreast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643–6.

26. Qin K, Wu C, Wu X. Two non synonymous polymorphisms (F311 and V571) of the STK15 gene and breast cancer risk: a meta-analysis based on 5966 cases and 7609 controls. J Int Med Res 2013;41:956–63.

27. Fletcher O, Johnson N, Palles C, et al. Inconsistent association between the STK15 F311 genetic polymorphism and breast cancer risk. J Natl Cancer Inst 2006;98:1014–8.
[29] Tang W, Qu H, Ding H, et al. Association between the STK15 F31I polymorphism and cancer susceptibility: a meta-analysis involving 43,626 subjects. PLoS One 2013;8:e82790.

[30] Dai Q, Cai QY, Shu XO, et al. Synergistic effects of STK15 gene polymorphisms and endogenous estrogen exposure in the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2004;13:2065–70.

[31] Liu Y, Sun B, Liu T, et al. Function of AURKA protein kinase in the formation of vasculogenic mimicry in triple-negative breast cancer stem cells. Onco Targets Ther 2016;9:3473–84.